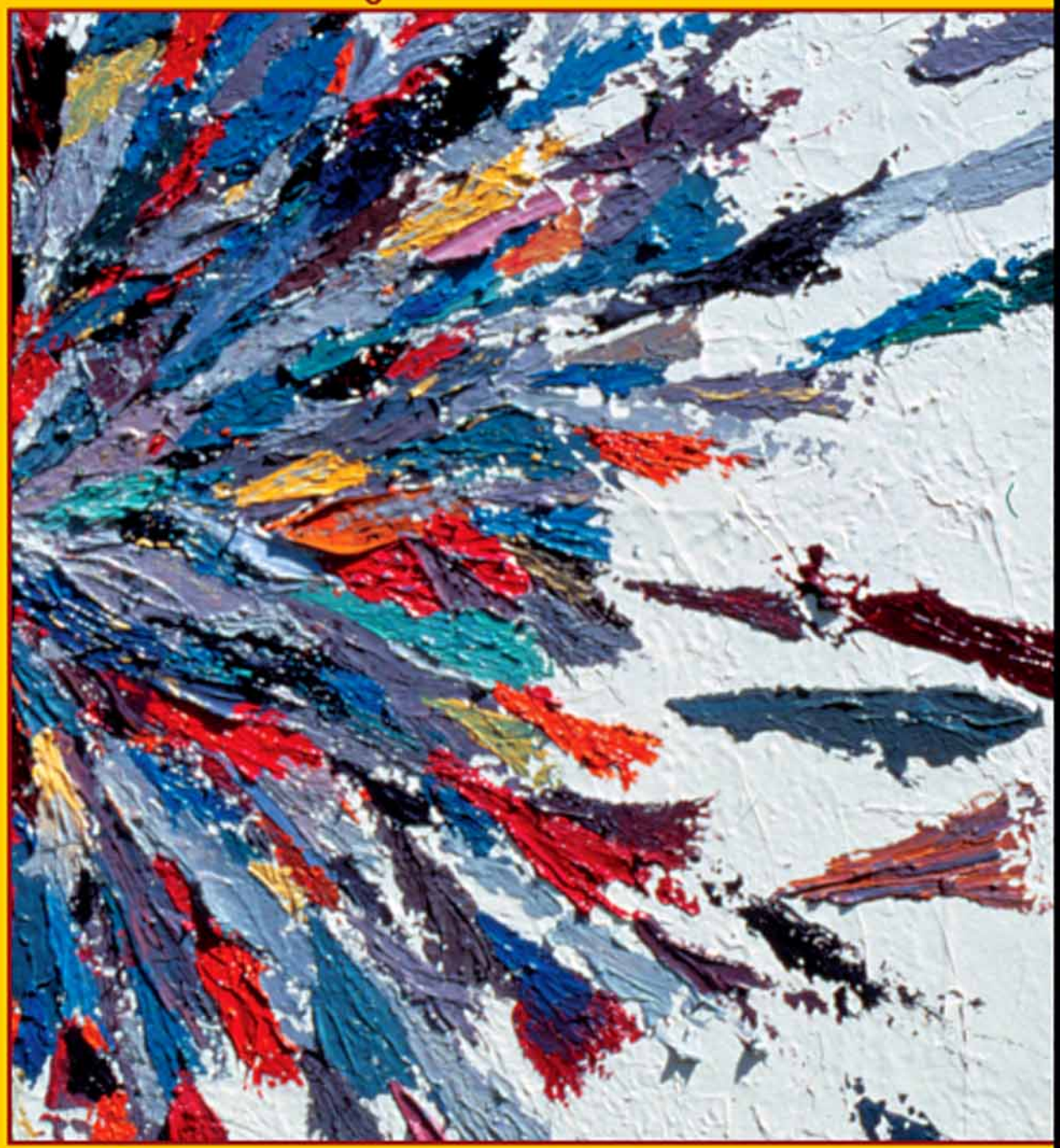
Cognition, Brain and Consciousness

Introduction to Cognitive Neuroscience



Second Edition

Bernard J. Baars and Nicole M. Gage

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SECOND EDITION

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BERNARD J. BAARS
NICOLE M. GAGE

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AMSTERDAM • BOSTON • HEIDELBERG • LONDON • NEW YORK • OXFORD
PARIS • SAN DIEGO • SAN FRANCISCO • SINGAPORE • SYDNEY • TOKYO
Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
525 B Street, Suite 1900, San Diego, California 92101-4495, USA
Elsevier, The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, UK

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Library of Congress Cataloging-in-Publication Data
Baars, Bernard J.
Cognition, brain, and consciousness : introduction to cognitive neuroscience/Bernard Baars, Nicole Gage. — 2nd ed.
p. cm.
Includes bibliographical references and index.
ISBN 978-0-12-375070-9 (hardcover : alk. paper) 1. Cognitive neuroscience. I. Gage, Nicole M. II. Title.
QP360.5.B33 2010
612.8'233—dc22

2009039469

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

ISBN:978-0-12-375070-9

For color figures, glossary, and study guide, please visit our companion website: www.baars-gage.com

For information on all Academic Press publications visit our Web site at www.elsevierdirect.com

Printed in China

10 11 12 9 8 7 6 5 4 3 2 1

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Preface

Keeping up-to-date with cognitive neuroscience is much like surfing the Big Wave at Waikiki Beach. New findings keep rolling in and maintaining a stable balance is a big challenge. It is exciting, fun, and, at times, a little bit scary. But we keep climbing back on our mental surfboards, to catch the coming rollers of advancing science. This book aims to provide an overview of the emerging science of mind and brain in a way that is accessible to students and interested readers at all levels.

For the Second Edition a number of new features have been added.

1. A new chapter on the *Genes and Molecules of Cognition* (Chapter 16) introduces essential new developments in the molecular basis of cognition. Neurons build links with other neurons by expressing proteins, directed by the genetic (and epigenetic) apparatus of the cell. Thus the molecular level has become essential for understanding learning, language, perception, thinking, and other basic functions. This chapter presents 'genes and molecules' in readily understandable ways.
2. A complete revision of the chapter on *Consciousness and Attention* (Chapter 8) takes into account the last ten years of research. New recording methods have led to remarkable breakthroughs. For example, brain rhythms have been shown to carry both conscious and unconscious information. The Second Edition is fully up-to-date on these findings.
3. A major revision of Chapter 12, *Goals, Executive Control, and Action* has been included. The frontal lobes have been called 'the organ of civilization' but they have long been viewed as mysterious. Many of the traditional puzzles are now clearing up, as this chapter explains, with a presentation of the current view of the organizing principles of the prefrontal cortex.
4. Individual scientists are presented in text boxes called *Frontiers in Cognitive Neurosciences.* These leading scientists from around the globe present their views about new directions and important findings in their discipline within the broader field of Cognitive Neuroscience:
   - Nelson Cowan, PhD, University of Missouri
   - David Eagleman, PhD, Baylor College of Medicine
   - Gerald Edelman, MD, The Neurosciences Institute
   - Paul Fletcher, PhD, University of Cambridge
   - Angela Friederici, PhD, Max Planck Institute for Human Cognitive and Brain Science
   - Christopher Frith, PhD, Wellcome Trust Centre for Neuroimaging
   - Christof Koch, PhD, Division of Biology, California Institute of Technology
   - Stephen L. Macknik, PhD, Barrow Neurological Institute
   - Susana Martinez-Conde, PhD, Barrow Neurological Institute
   - Aniruddh Patel, PhD, The Neurosciences Institute
   - Charan Ranganath, PhD, University of California, Davis
   - Michael Rugg, PhD. University of California, Irvine
   - Jenny Saffran, PhD, University of Wisconsin, Madison
   - Larry Squire, MD, University of California, San Diego School of Medicine
5. A new Glossary of technical terms has been added. Since vocabulary is one of the great challenges in learning cognitive neuroscience, we expect the Glossary to be a basic tool for students and instructors.

6 A new Mini-Atlas of the Human Brain has been added in pullout form at the front of the book. Knowing one's way around the brain is the first step in understanding the mind-brain sciences. But the brain is simply enormous in complexity and topographical knottiness. In the First Edition we used illustrations from *Gray's Anatomy* and other Elsevier/Academic Press sources to create a lavishly illustrated text. The Second Edition adds a Mini-Atlas to give newcomers even more support to explore the landscape of the brain – a compass and map of the territory.

7 The Appendix on Brain Imaging Methods has been completely updated by an expert in that field, Dr. Thomas Ramsoy of the University of Copenhagen.

As Christopher Frith, Michael Posner, and others have written, we are seeing a marriage of the cognitive and brain sciences, building on historic advances over the past few decades. Cognitive and perceptual mechanisms that were inferred from behavior can now be observed more directly in the brain, using a variety of novel brain imaging methods. For the first time, we can observe the living brain in real time, doing what it has evolved to do over hundreds of millions of years. The result is astonishingly rich, combining psychology and biology, medicine, biochemistry, and physics. Yet most scientific studies use well-established psychological concepts and methods. As a result, we are now seeing how psychology and brain science complement each other in surprising and gratifying ways. The field of *cognitive neuroscience* is becoming a basic educational requirement in psychology, biology, education, and medicine.

Cognitive neuroscience has been difficult to cover in a single course. Many instructors discover that they spend most of the term explaining the brain, with little time left for integrative topics. While understanding the brain is vital, an exclusive focus on anatomy can defeat the instructors' objectives.

This text approaches that challenge in several ways. First, the body of the text follows the gentlest learning curve possible, running along familiar lines: sensory perception in vision and audition, working memory, attention and consciousness, memory, executive functions, language and imagery, problem solving, emotion, social cognition, and development. The brain is introduced step by step, with gradually increasing sophistication. To make sense of the material we use a *functional framework* throughout the book. This widely accepted set of ideas allows us to see our major topics in a single schematic diagram, which grows in depth and detail over the course of the book. The functional framework can be seen from different perspectives. For example, memory stores may be viewed from an active working memory perspective; or perception, cognition, and control may be seen as playing upon permanently stored information in the brain (Chapter 2). The framework helps either way.

A website for teachers and students is available at http://textbooks.elsevier.com via a free registration. Supportive materials for teachers include all figures and captions from the book in powerpoint format, as well as instructional video and multimedia files. Student materials include chapter reviews, quizzes, figures, and videos. The support site will be dynamic. Materials will be added and changed as warranted by new advances, and the authors are happy to consider additional ideas and suggestions for new supportive materials.

Instructors may present the chapters in any order that suits their goals. For advanced students, Chapters 4 and 5 on brain imaging and anatomy may be covered lightly. For introductory courses those chapters are essential and may be supplemented with the more challenging appendix (by Thomas Ramsøy and colleagues). The appendix can also be used as a convenient reference sources.

A full range of brain disorders are covered, from HM and the case of Clive Wearing (Chapters 2 and 9), to blindsight, visual neglect, face blindness and other visual deficits (Chapter 6). Chapter 11 on executive function covers disorders of undercontrol and overcontrol. In certain disorders, motor and cognitive control is not directly impaired at all; it seems as if patients are just not willing to act. At the other pole, patients sometimes spontaneously imitate another person's actions as if they cannot stop themselves. Such patients may stand up impulsively when the examining physician stands up. Disorders of overcontrol and undercontrol reveal basic aspects of human executive functioning.

Some disorders have close psychological analogs. Professional musicians, like pianist Van Cliburn, are sometimes unable to inhibit their tendency to sing along with instrumental playing. Highly trained experts can lose some executive control over automatic behaviors, especially if they are working under mental workload. On the opposite side, a classic symptom of severe depression is that patients seem unable to initiate and pursue actions. Brain regions involved in such 'purely psychological' deficits are often implicated in similar organic disorders. We see another striking

simplification of the evidence, giving readers a chance to understand unifying principles rather than scattered facts.

Psychological topics are often simplified by brain evidence. For example, the verbal part of classical working memory – the capacity mentally to rehearse numbers and words – is now thought to be a part of our normal language capacity. Baddeley (2003) has emphasized the discovery that silent rehearsal activates the well-known speech regions of cortex. Thus the 'phonological loop' of traditional working memory is no longer seen as a separate cognitive feature, but rather as a silent way of using speech cortex. Similarly, Kosslyn and others have shown that visual imagery makes use of a subset of the cortical areas involved in normal visual perception (2004). Even more surprising, visual attention appears to be closely related to eye movement control. Athletes and musicians use the sensorimotor brain to engage in silent mental practice. Thus 'inner' and 'outer' processes seem to involve overlapping regions of the brain, a major simplification of the evidence.

While cognitive neuroscience does not always simplify things, it does so often enough to allow us to organize this text along recurring themes. This makes the material easier to teach and understand. It allows us to explore a wide range of basic topics, including emotion, social cognition, and development.

The companion materials are designed to enrich student learning by way of vivid classroom demonstrations, images, and learning points, using Powerpoint presentations and movie clips. A number of phenomena in the text can be best illustrated by way of experiments and movie clips. For example, a patient is shown with locked-in syndrome, able to communicate only by means of eye movements directed at a keyboard display. For comparison, we show patients who look superficially the same, but who are suffering from true coma.

At the end of each chapter, review questions and brain drawing exercises are designed to help students learn interactively. We particularly emphasize drawing and coloring exercises as a way to grasp the knotty three-dimensional organization of the brain.

This text covers some frontier topics in the ever-changing vista of cognitive neuroscience. One popular topic is the relationship of 'the mind' as we experience it and 'the brain' as we observe it: i.e. the historic topic of consciousness and its brain correlates. Alan Baddeley recently noted that, 'Perhaps the greatest change over the last twenty years within cognitive psychology and cognitive science . . . has been the acceptance of consciousness as a legitimate and tractable scientific problem'.

The renewed acceptance of consciousness has changed research in perception, memory, and attention, as seen in pioneering work by Endel Tulving, Daniel Shachter, Gerald Edelman, Francis Crick, Christof Koch, and numerous others. While some textbooks have added chapters on consciousness, we believe that the topic has now become so pervasive that it needs to be addressed throughout. As *Science* journal recently noted in its 125th anniversary issue, consciousness is now thought to be one of the major unsolved problems in biological science. While much remains to be learned, psychologists have long studied conscious processes under such headings as 'explicit cognition' and 'focal attention'. Those constructs are all assessed by the behavioral index of accurate report, which has been taken to signal conscious events since the beginning of psychophysics, some two centuries ago. Thus 'consciousness' can be seen as an umbrella label, much like 'memory' and 'perception', with a number of subtopics like subliminal perception, autobiographical memory, and focal attention.

Voluntary control is also back on the forefront of research, sometimes under the rubric of 'strategic control' and 'executive functions'. In the brain, voluntary and non-voluntary functions can be clearly distinguished anatomically and physiologically. Robust differences also appear in functional brain imaging and behavior. Finally, the notion of executive control appears to be moving toward new insights on the 'self' of everyday life, as studied in social and personality psychology.

All these topics show a striking convergence of behavioral and brain evidence.

The brain basis of emotion and social relationships is developing as well. 'Mirror neurons' are involved with the ability to perceive intentions in others; unconscious 'threat faces' can stimulate the amygdala; and conflicting aspects of self-control are apparently played out in competing impulses in prefrontal cortex.

Cognitive neuroscience is challenging; it is also one of the most important frontiers in science. Students will be rewarded with a new depth of understanding of human nature, one that has never been quite as clear and convincing as it is today.

The editors are especially grateful to Dr. Johannes Menzel, Publisher, Science Solutions and Content Strategy, Elsevier Publishers. We are also very grateful to Clare Caruana, Development Editor, Life Science

Books, Academic Press, Elsevier, for her guidance and support throughout our efforts for this Second Edition. During the preparation for our Second Edition, Johannes and Clare moved on to new and greater challenges at Elsevier and we welcomed Mica Haley, Senior Acquisitions Editor, and Melissa Turner, Development Editor, to our team. Mica and Melissa picked up the Second Edition and seamlessly guided us through the complex stages of producing a large text. We are grateful for all of their efforts on our behalf. We appreciate their consistent kindness, advice, and support throughout a very challenging project. Indeed, the current text would have been impossible without the vast archival resources of Elsevier.

We are grateful for our many contributors who added their expertise to this volume:

Daniela Balslev
Danish Research Centre for Magnetic Resonance, Hvidovre Hospital, Denmark

Dmitri Bougakov
Department of Neurology, New York University School of Medicine, New York, New York, USA

Jason M. Chein
Psychology Department, Temple University, Philadelphia, Pennsylvania, USA

Melanie Cohn
Department of Psychology, University of Toronto, Ontario, Canada

Elkhonon Goldberg
Department of Neurology, New York University School of Medicine, New York, New York, USA

Mark H. Johnson
Center of Brain and Cognitive Development, School of Psychology, Birkbeck College, London, UK

Katharine McGovern
California Institute for Integrative Studies, San Francisco, California, USA

Morris Moscovitch
Department of Psychology, University of Toronto, Toronto, and Baycrest Center for Geriatric Care, Rotman Research Institute, North York, Ontario, Canada

Olaf Paulson
Danish Research Centre for Magnetic Resonance, Hvidovre Hospital, Denmark

Joel Pearson
Department of Psychology, Vanderbilt University, Nashville, Tennessee, USA

Thomas Ramsøy
Danish Research Centre for Magnetic Resonance, Hvidovre Hospital, Denmark

Deborah Talmi
Department of Psychology, University of Toronto, Toronto, Ontario, Canada

Frank Tong
Department of Psychology, Vanderbilt University, Nashville, Tennessee, USA

The first editor is particularly grateful to Dr. Gerald Edelman and his colleagues at the Neurosciences Institute in San Diego, as a unique source of insight and collegial guidance on many topics in neuroscience. He is also indebted to the Mind Science Foundation of San Antonio, Texas, for supporting pioneering explorations in the cognitive neuroscience of consciousness. MSF's Board and Executive Director, Joseph Dial, have been especially active in working to unify behavioral and brain approaches to conscious experience (www.mindscience.org).

A number of colleagues and friends have helped us to gain a deeper understanding of mind and brain. There are too many to list here, but we want them to know of our gratitude. Among recent colleagues, Stan Franklin, Walter Freeman, William P. Banks, E. R. John, Christof Koch, Francis Crick, Karl Pribram, Dan Dennett, Patricia Churchland, Patrick Wilken, Geraint Rees, Chris Frith, Stan Dehaene, Bjorn Merker, Jaak Panksepp, Stu Hameroff, Thomas Ramsøy, Antti Revonsuo, Michael Pare, Henry Montandon, Murray Shanahan, and many others have helped us to think through the issues. We have not always agreed, but we have always felt grateful for their constantly interesting and important ideas.

We have been fortunate to have the help of outstanding co-authors for this book. Their contributions are acknowledged in the Contents. This book would be poorer without their depth of knowledge and desire to communicate.

In a broader but very real sense, this book owes everything to the community of scholars and scientists who are cited in its pages.

In more personal terms, the first editor would like to acknowledge his loved ones for putting up with him during this daunting project. His parents, now deceased, are still a constant source of inspiration and

guidance. He would also like to express his gratitude to Dr. Barbara Colton for constant feedback and support, which have made the book much more readable and the editor far more sensible.

Ms. Blair Davis was invaluable in helping to put this book through its final stages. Mr. Shawn Fu provided a number of beautiful brain illustrations.

The second editor is particularly grateful to the first editor for sharing his concept and passion for this project. Our collaboration on this text began a few years ago during a 3-hour layover in Chicago and has blossomed into this full-blown project, along with a strong friendship. She is also indebted to many colleagues and friends with whom she has learned about how language gets wired up in the brain. There are too many to include here, but she is indebted to them all. She is particularly grateful to Greg Hickok, David Poeppel, Larry Cahill, Norm Weinberger, Bryna Siegal, Anne Spence, and Kourosh Saberi for good conversations, ongoing debates, and thoughtful discussions through the years.

The second editor would like to acknowledge her family for their constant support during this project. Last, she is indebted to Kim for his insight and love.

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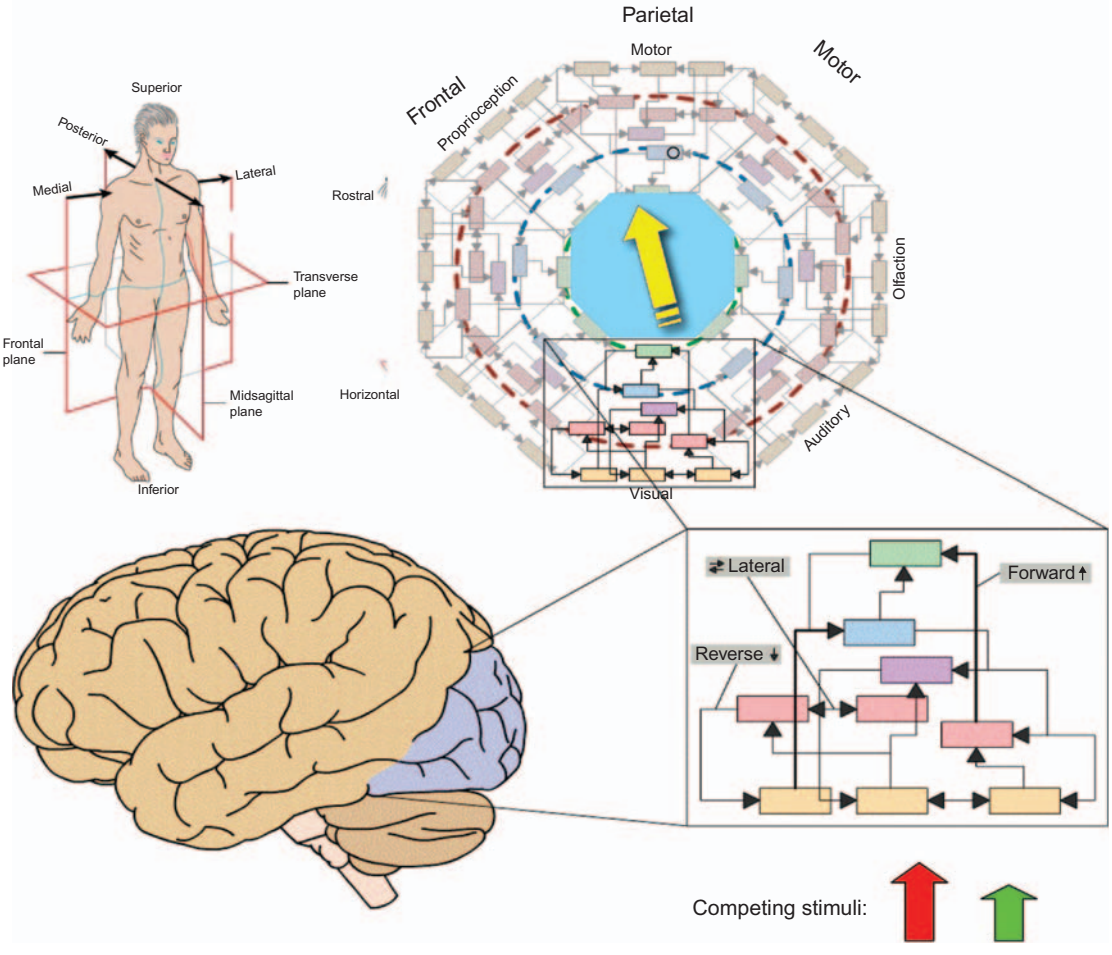
COGNITION, BRAIN, AND CONSCIOUSNESS

SECOND EDITION

. . . from the brain, and from the brain alone, arise our pleasures, joys, laughter and jokes, as well as our sorrows, pains, griefs and tears. Through it, in particular, we think, see, hear, and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant . . . all the time the brain is quiet, a man can think properly.

Attributed to Hippocrates, 5th century BCE
(quoted by Kandel *et al.*, 1991).



Upper left: The human body and its basic orientation planes. *Lower left*: A standard view of the brain from the left side. The left hemisphere is 'looking' left. The light blue region in the back of the brain is the occipital lobe. The diagram on the lower right shows a 'neural hierarchy', a simplified way of showing neural connections in the cortex, and on the upper right we see the entire cortex as a 'circle of hierarchies'. The yellow arrow in the center depicts a common view of the role of perceptual consciousness in the brain. *Source*: Drake *et al.*, 2005.

CHAPTER

1

Mind and brain

OUTLINE

1.0 INTRODUCTION

This chapter gives an overview of cognitive neuroscience, the combined study of mind and brain. The brain is said to be the most complex structure in the known universe – with tens of billions of neurons, connected by trillions of transmission points. It can be changed by taking in molecules, as in drinking a glass of wine, and by external stimulation, like listening to exciting news. Some neuronal events happen over a thousandth of a second, while others take decades. In spite of this vast range of working conditions, we know many facts about the mind-brain that are basic and fairly simple. This book aims to let those facts stand out.

2.0 AN INVITATION TO MIND-BRAIN SCIENCE

It is hard to talk about the last dozen years in cognitive neuroscience without using words like 'remarkable' and 'revolutionary'. In a sense, a century of behavioral and brain science has received resounding confirmation with the new technology of brain imaging, the ability to observe the living brain in real time. That

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

FIGURE 1.1 Rembrandt, The Anatomy Lesson of Dr. Tulp. This historic painting by Rembrandt shows the excitement of the first revolution in scientific thinking about the human brain and body. Dr. Tulp, on the right, is demonstrating how the muscles of the forearm control hand movements. The systematic dissection of human cadavers signaled a rebirth of careful empirical observation which still guides us today. *Source*: Masquelet, 2005.

does not mean, of course, that we have merely confirmed what we thought we knew. Rather, the ability to record from the living brain has proved to be fruitful in bringing out new evidence, raising new ideas and stirring new questions. Many scientists have a sense that a great barrier – between the study of mind and brain – is being bridged. Historically tangled questions continue to yield quite beautiful insights.

Along with this feeling of progress has come a great expansion. Just 10 years ago, behavioral scientists might not have seen a connection between human cognition and the genetic revolution, with brain molecules, or with the mathematics of networks. Today, those topics are all part of a connected island chain of knowledge. Previously avoided topics are now anchored in plausible brain correlates – topics like conscious experience, unconscious processes, mental imagery, voluntary control, intuitions, emotions, and even the self. Some puzzles seem bigger than before – the nature of the permanent memory trace, for example. There seem to be more continuities than ever before between psychological and brain studies of perception, memory, and language.

In some cases, brain evidence helps to resolve puzzles that psychologists have wrestled with for decades. For example, in the study of attention a debate has raged between 'early' and 'late selection' of attended information. People may pay attention to a coffee cup based on low-level visual features like color, texture and location. Alternatively, they might focus on the coffee cup based on higher-level properties like 'usefulness for drinking hot liquids'. Evidence can be found for both. After decades of debate, brain studies have now shown that attentional selection can affect neurons at almost *any* level of the visual system. The answer therefore seems to be that there can be *both* early and late selection, as many psychologists have also argued. In many cases like this we find surprising convergence between brain and behavioral evidence.

3.0 SOME STARTING POINTS

3.1 Distance: seven orders of magnitude

To understand the mind-brain, it helps to have an idea of its orders of magnitude, the powers of ten that tell us the basic units of interest. From front to back, a brain is perhaps a seventh of a meter long. If you take one step, the length of your stride is about one meter (a little more than a yard). If you raise that length to the next order of magnitude, 10 meters, you might obtain the rough length of a classroom. One hundred meters is a standard sprinting distance, and a thousand meters or one kilometer is a reasonable length for a city street. By the time we raise the exponent to 10^7 meters, or 10 000 km, we are already at 6000 miles, the distance from coast to coast in North America, or from Paris to the equator in Europe and Africa. That is ten million steps. In order to understand the most

TABLE 1.1 Distance from 10^{-7} m to one meter

1 If you drink alcohol your brain will change. Alcohol molecules are about 10^{-7} meters in size (Figure 1.2) (0.0000001).
2 If you swallow a tranquillizer, the chemical concentration that flows across some of your synapses will be changed, at 10^{-6} m for the width of a synapse (one-millionth of a meter, or one micron).
3 The cell bodies of neurons are about a hundred times larger than synapses, around 10^{-4}.
4 However, neurons do not act alone; they are grouped with others in small networks, perhaps ten times larger than single neurons. Small cortical columns are about 10^{-3} m or one millimeter in diameter. We have now reached one-thousandth of a meter, which we can see with the naked eye.
5 Brain maps, such as those in the visual system, can be quite large. The first cortical map of the light array is called area V1, the first visual region of cortex. It is about the size of a credit card, several square centimeters in size, or $10^{-2}\,m^2$.
6 Visual maps don't work in isolation. They are part of brain-wide activation networks that interact in constantly changing patterns. Such widespread networks operate at an order of magnitude of ten centimeters (10^{-1}), well inside the visible range if you could see brain activity through the scalp. Indeed, some current methods observe the brain's constantly varying activity by simply shining a laser through the shaved scalp of rats or other small mammals. One can watch the flow of blood to brain surfaces that are active, just as we can see increased blood flow to the skin when people have been running hard.

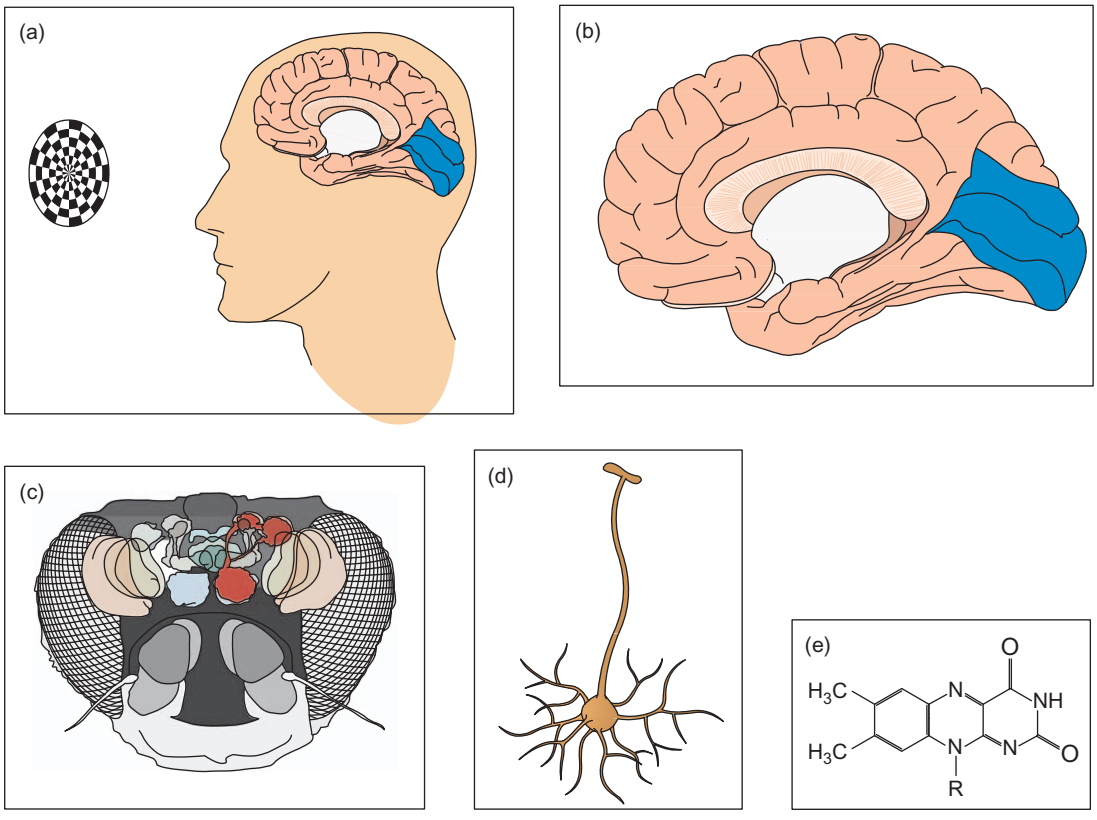


FIGURE 1.2 Spatial powers of ten. (a) A brain image of a subject looking at a rotating black and white stimulus, so that his visual cortex (in the rear of the brain) is intensely stimulated. (b) A midline view of the cortex, with area V1 marked – the first place where the visual pathway reaches cortex. V1 is about the size of a credit card. (c) The head of a fruit fly. The fruit fly brain has about 1 000 000 neurons. A single neuron is shown in (d). Neurons vary in size, but they are extraordinarily small; we have tens of billions in our brains. (e) A dopamine molecule. Dopamine plays an essential role in working memory, in the experience of pleasure, and in the control of muscles. Parkinson's disease is one result of a decline of the dopamine system. From (a) to (e), the range of sizes involves about seven orders of magnitude.

important magnitudes of the brain we can simply imagine going the other way, seven orders of magnitude from one meter to 10^{-7} (Table 1.1). Considered this way it is an awesome prospect in size and complexity.

Visible behavior takes place anywhere from a centimeter and up. A finger striking a keyboard moves only a few centimeters. When we speak, our tongue moves only a centimeter or two. A single walking step is about a meter long. Most people are a little less than

FIGURE 1.3 Small molecules can change the brain. Some of the smallest molecules like nitrous oxide (N_2O) can change specific brain functions. That came as a big surprise to Western medical doctors around 1800, like the ones above, shown in a drawing by a medical student in 1808. However, such facts continue to surprise us. Nitric oxide (NO), which is toxic when breathed, is produced in tiny quantities as a crucial neurotransmitter. The erectile drug, Viagra, promotes NO transmission in penile blood vessels. *Source*: Adelman and Smith, 2004.

two meters in height, and the longest neurons in the human body may be about 1 meter.

3.1.1 A note about neurochemicals: the smallest level

Neurotransmitters range in size, and diffuse across gaps between neurons – the synapses – which vary between 25 nanometers to 100 micrometers (Iversen, 2004). Most brain-changing chemicals promote or block molecular communication between nerve cells. The list of everyday chemicals that change the brain includes nicotine, alcohol, oxygen (in the air), toxic gases like carbon monoxide, glucose from the liver and sucrose from foods, chocolate, coffee, nerve toxins like lead, and a long list of medications (Figure 1.3). It is hard to overstate the importance of such molecules in everyday life.

Molecular messengers in the brain can be divided into two large groups. The first group, the neuromodulators, are 'sprayed' throughout large parts of the forebrain from small fountain-like clumps of cell bodies at the base of the brain. These are informally called 'spritzers', because they secrete neurochemicals from widely dispersed axons, to modulate large parts of the brain. However, neuromodulators can have local effects if they lock into specific types of local receptors. For example, while dopamine is spread very widely, the D1/D2 dopamine receptors are believed to have local effects in the frontal cortex related to working memory (Gibbs and D'Esposito, 2006). Thus, a very wide-spread neuro-modulator, dopamine, can have more local effects when it locks into receptors in a specific region of the brain.

The second major group of neurotransmitters have much more localized actions. They are mostly peptides, i.e. small subunits of proteins, which are secreted directly into synaptic gaps. More than 40 types of neuropeptides have now been found throughout the brain. The two best-known examples are *glutamate*, the most widespread excitatory neurotransmitter in the cortex, and *GABA*, the most common inhibitory neurotransmitter.

Scientific advances often follow our ability to observe at different magnitudes. The wave of discoveries we are seeing today results from our new ability to observe the living brain. The ability to observe over some seven orders of spatial magnitude makes mind-brain science possible.

3.2 Time: ten orders of magnitude

Human beings function over a great range of time scales (Table 1.2). Behaviorally, one-tenth of a second (100 ms) is an important unit to keep in mind. The fastest (simple) reaction time to a stimulus is about 100 milliseconds, and the time it takes for a sensory stimulus to become conscious is typically a few hundred milliseconds. This makes sense in the environment in which human beings

TABLE 1.2 Time: Ten orders of magnitude, from years to milliseconds

1 When you listen to a high musical note, your auditory nerve is firing as fast as the sound waves that vibrate your ear drum, up to 1000 times per second, or one wave per millisecond (ms). (Reminder: cycles per second = Hertz = Hz).
2 Neurons can fire as fast as 1000 Hz, although the average neuron in the cortex fires about ten times per second.
3 The auditory nerve is a bundle of nerve axons, each of which fires slower than 1000 cycles per second, but together they can respond at millisecond speed. Some sensory events are even faster. In a remarkable feat, our brain can distinguish differences between sounds arriving at the two ears, down to several *microseconds*, or millionths of a second. That is 1000 times faster than the fastest firing rate of a neuron (see Chapter 7). However, for our purposes, milliseconds are the most useful unit at the small end of the time scale.
4 By comparison, if you count to yourself from one to ten, your counting takes place on the order of seconds, or tens of seconds. If you study this chapter carefully, it will take you an hour or more – more than three thousand seconds. (Sorry about that!)
5 Going back down the scale again, if the sound track of a movie is delayed by a fraction of a second behind the video, you will notice a disconnect between the sounds and the movements of an actor's mouth. The break-up of audio-visual synchrony occurs after about 100 milliseconds (ms) lag, or one-tenth of a second. This is another reason to think of one-tenth of a second as a special order of magnitude.
6 One hundred milliseconds is also about the fastest we can react to an event that we know will come soon, as in starting a car at a traffic light (*simple reaction time*). One-tenth of a second is also about the rate of individual alpha and theta waves in the brain. (Alpha waves range between 8–12 Hz, and theta between 5–7 Hz.) It is also the order of magnitude required to become conscious of a sensory stimulus.

evolved. If you took several seconds to react to a hungry predator, you will soon provide it with a tasty protein snack. Biologically, you would not get a chance to reproduce. On the other hand, if you tried to react as fast as 10 milliseconds – one-hundredth of a second – you would be driving your brain faster than it could combine the sights and sounds of a running tiger. It would be hard to tell what direction a predator might be coming from. So the 100 ms range gives a useful middle ground.

Brain events at different time and spatial scales go on at the same time, like the elements of a symphony – notes, phrases, and whole musical movements. When you listen to a song, you are conscious of only a few notes at any time, but the notes you hear fit into a larger cognitive structure which makes it possible to appreciate how the entire song is developing. Movie frames are shown at 24 images per second, or about 40 milliseconds per frame, to show smooth movement. (That's why they call them movies!) Slower rates than 24 Hz start to look jerky, like the early silent movies. However, the plot of a movie takes place over minutes and hours. In a mystery film, if you cannot remember the crime at the beginning, the fact that the perpetrator is found at the end will not make sense. Thus, understanding movie plots requires cognitive integration over many minutes. All these time scales must somehow be combined. Each kind has a structure and a typical time range. The brain keeps track of all simultaneously.

At the longer end of the time scale, it can take years to learn a difficult skill, like skiing or playing guitar. Infants learn their first language over several years, while adults tend to keep their basic personality structure over decades. Such long-term processes depend upon the same brain as 100-millisecond events. In the time domain, therefore, we need to understand about ten orders of magnitude, from one-thousandth of a second (a millisecond) for a single neuron to fire, to more than 100 000 seconds per day, and tens of millions of seconds per year.

3.3 The need to make inferences – going beyond the raw observations

Science depends on a constant process of inference, going from raw observations to explanatory concepts. Thousands of years ago, when human beings began to wonder about lights in the sky like the sun, the moon, and the stars, they noticed that some were predictable and some were not. The 'wanderers' in the night sky were called *planete* by the Greeks, and we call them 'planets' in English. These wandering lights became a source of fascination. It was not until the 17th century that their paths were understood and predicted. The solution to the wandering lights puzzle was to realize that the planets were giant earth-like spheres revolving in orbit around the biggest object of them all, the sun. It took centuries of argument and observation to settle on that solution. Isaac Newton had to invent the infinitesimal calculus to bring the debate down to a simple equation: planetary orbits can be predicted from the simple fact that gravitational force equals the mass of the orbiting planet times its acceleration. Notice that all those words – 'sun', 'planet', 'force', and 'gravity' – are *inferred concepts*. They are far removed from the first observations of lights in the sky (Figure 1.4), yet they explain those raw observations: they are explanatory inferences.

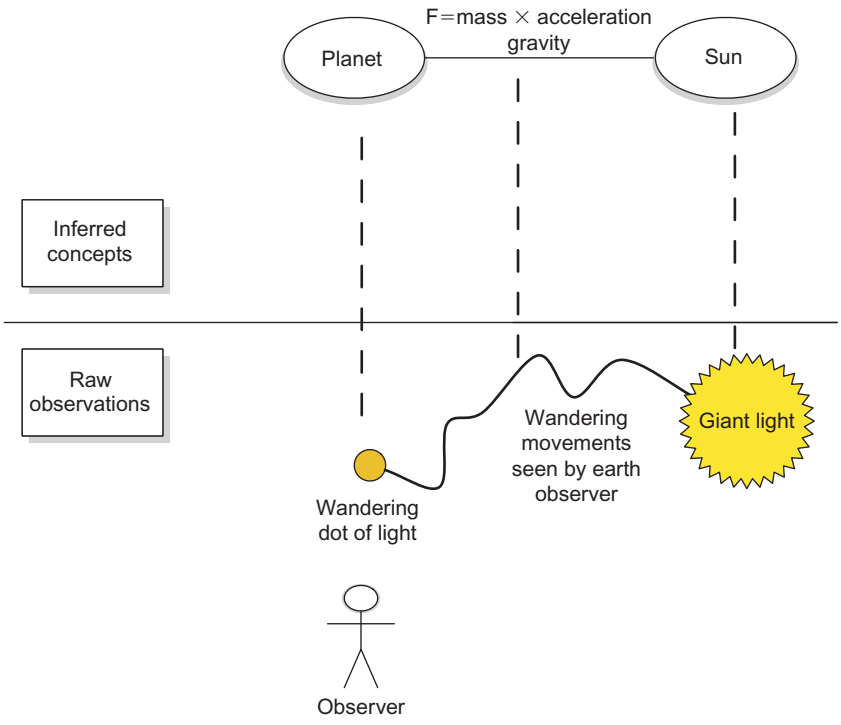


FIGURE 1.4 Making inferences about lights in the night sky. To an earthbound observer the planets look like wandering lights in the night sky. After many years of careful astronomical observations, Isaac Newton and others determined that the complex wandering path of the planets reflects a very simple reality. The leap from raw observation to inferred concepts and explanations is a crucial part of science.

All science depends upon careful observations and conceptual inferences. The resulting explanatory framework has been called a 'nomological network' – that is, a network of labeled concepts and relationships, which together provide us a sense of understanding. Along the way, successful science allows us to make more accurate predictions, and to apply the resulting knowledge in ways that sometimes transform life. It all begins with exact observations and plausible inferences.

These basic ideas have a direct bearing on cognitive neuroscience. When we talk about cognition – language, learning, or vision – we also use *inferred concepts*, which must be firmly anchored in reliable observations. For example, the capacity of immediate memory – the kind we can mentally rehearse – is about seven plus or minus two items, as George A. Miller famously noted in a paper called 'The magical number seven plus or minus two' (1956). That number seems to apply to many kinds of randomly selected items: colors, numbers, short words, musical notes, steps on a rating scale, and so on. The recent consensus is that the actual capacity of immediate memory is even less than seven, about four different items (Cowan, 2001). But the most important point is the remarkable consistency in the data. Try to remember ten different foods on your shopping list, for example, and you will find that only about seven are remembered – and if you are busy thinking about other things, that number drops to four. It is an amazingly narrow limit for a giant brain.

There are only a few basic conditions for obtaining the size of working memory. One is that each item must be attended for only a brief time – perhaps several seconds – so that it cannot be memorized well enough to enter permanent memory. A second condition is that the items must be *unpredictable* from existing knowledge. If we ask people to remember a regular number series like 0, 5, 10, 15, 20, 25 . . . they only need to remember the rule, and it will seem that their working memory capacity is endless. Cognitive concepts like 'working memory' are the product of decades of experimental observations which finally become so solid that we can summarize the evidence in one basic concept (Figure 1.5).

Ideas like working memory have turned out to be useful, but it is quite possible that we will find a more attractive way to think about them tomorrow. All inferred concepts are somewhat tentative. Newton's idea of gravity dominated physics for three centuries, then Einstein found another way to look at the evidence. Scientific concepts are not metaphysical certainties. They are always subject to revision.

Cognitive neuroscience is also based on inferences from raw observations. Because brain scans have the appearance of physical objects that we can see and

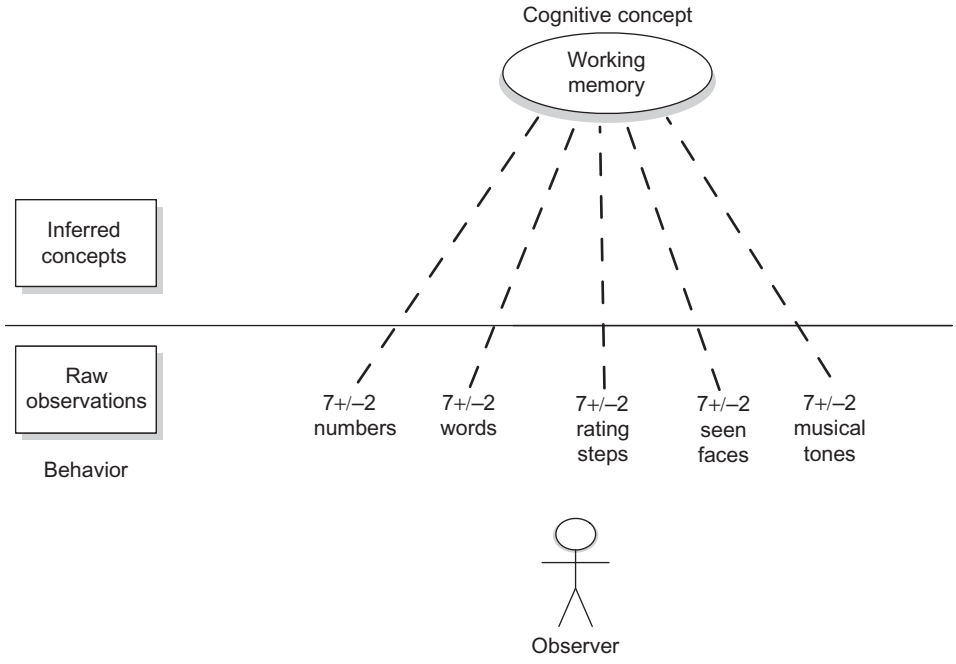


FIGURE 1.5 Cognitive concepts are based on consistent behavioral observations. Concepts like 'working memory' are not given in nature. They emerge after many years of testing, when a large body of evidence seems to be explained by an inferred concept. Working memory was proposed in 1974 after two decades of study of immediate memory. Today it has expanded in scope, so that visual, verbal, and other temporary buffers are called working memories.

BOX 1.1 Imaging the living brain

The very idea of observing the living brain in action was unimaginable a decade or two ago. Methods from physics and molecular biology have been applied to the formidable problem of recording brain activity. A perfect method would be able to follow tens of billions of neurons, and sample each one a thousand times per second. It should then be possible to track the constantly shifting interplay between smaller and larger groups of neurons, involving trillions of possible connections. By analogy, a perfect spy satellite in orbit around the earth would be able to see every single human being, as well as the changing relationships between individuals and groups, from families to entire nations.

Such a perfect method does not exist. Our understanding of the brain is a kind of collage of many fragments of the puzzle, glued together to make a reasonable picture of the whole. But thinking about a perfect observation method gives us the parameters we might aim for.

Brain imaging has been a breakthrough technology for cognitive neuroscience, adding new evidence to decades of cognitive psychology, behavioral conditioning methods, psychophysics and fundamental brain science. Before these techniques matured, our knowledge came from animal studies and from the haphazard injuries incurred by human beings. But brain injuries are extremely imprecise, and even to describe the damage, neurologists often had to rely on post-mortem examination of patients' brains. The brain can often compensate for injuries, and lesions change over time as cells die and adaptation occurs, so that post-mortems do not necessarily reflect the injury at the time of diagnosis. Animal studies relied on presumed homologies – i.e. similarities across species – which were often not persuasive to everybody. No other animals besides humans have language and other distinctive human specializations. It was therefore very difficult to understand brain functions.

Many of those problems were resolved when it became possible to observe the living human brain, first by electroencephalography (EEG), then by X rays, then computer tomography (the study of slices – from the Greek word for 'slice', *tomos* – based on X-rays). Today, we have more than a dozen techniques that are rapidly evolving toward greater precision and a broader range of application. The most widely used methods are EEG, positron emission tomography (PET), magnetic resonance imaging (MRI), functional MRI, and magnetoencephalography (MEG). See Chapter 4 for a detailed description of these and other new techniques for investigating the dynamic human brain.

touch, we are tempted to think that we are seeing 'raw reality' in brain scans. But that is a seductive fallacy. Electroencephalography (EEG) is an inferential measurement of brain activity, as is functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and all the other advanced tools we have today (Box 1.1). Even recording from neurons only gives us a tiny sample of single cell firing among tens of billions of cells. Neurons make perhaps ten thousand connections, and there is evidence that even the input branches of a single neuron (the dendrites) may compute information (Alle and Geiger, 2006).

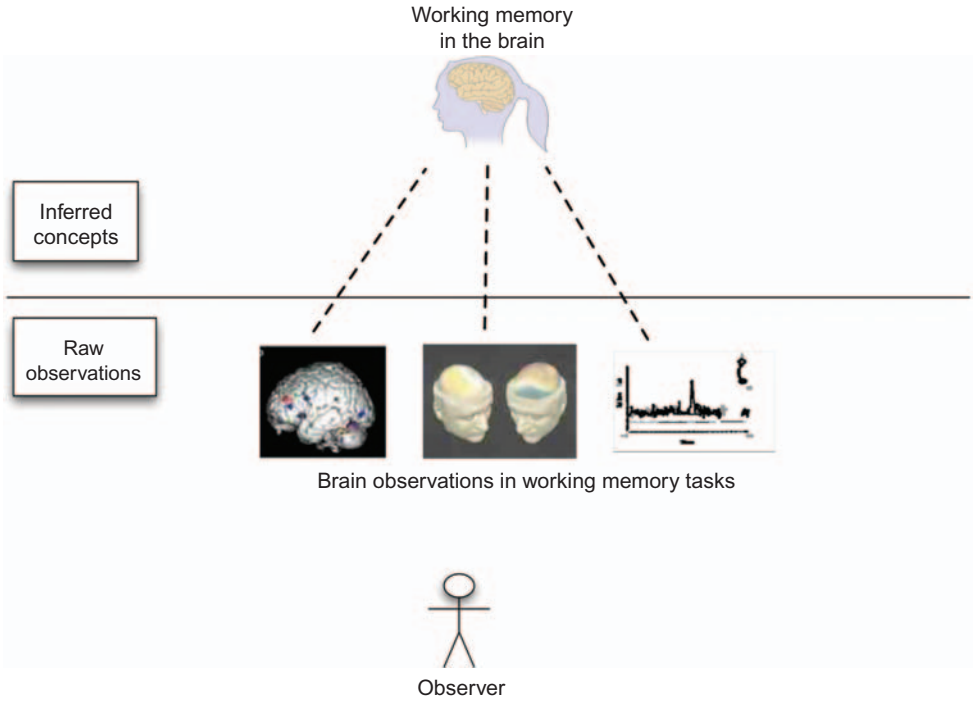


FIGURE 1.6 Brain measures of working memory are also inferential. Working memory functions in the brain have been studied using behavioral measures, but also with fMRI, EEG, and single-neuron recordings. Each of these measures has its pros and cons, but none of them is the 'ultimate measure' of working memory. Overall, brain indices of working memory converge well with behavioral measures. Cognitive neuroscience is based on the study of such combined sources of evidence, but we must be prepared to find that our current concepts may be interpreted in a different way.

Therefore, measuring the electrical activity of single neurons is only a tiny sample of a very complex dance of molecules and electromagnetic fluxes. Recent imaging techniques are extraordinarily useful, but they still involve inferences about the working brain.

Yet we must make *some* simplifying assumptions – that is how science develops. It is just important to keep in mind what the assumptions are, and to be prepared to change them if necessary. Figure 1.6 illustrates this point. In cognitive neuroscience we make inferences based on behavioral and brain observations. We don't *observe* 'attention' or 'working memory' directly. For that reason, it is essential to understand the nature of the evidence that we use to make those inferences.

3.4 The importance of convergent measures

When that mythical first cave dweller pointed to a star at night, we can imagine that nobody else in the clan believed him or her. What lights in the sky? The sky was the abode of the gods; everybody knew that. That kind of skepticism is the norm. When Galileo first used a crude telescope to look at the moons of Jupiter, some critics refused to look through the telescope, since they held that only the naked eye could tell the truth. Skepticism is still the norm, and science always makes use of *converging measures* to verify observations. Today, any major hypothesis in cognitive neuroscience is tested over and over again, using single-neuron recordings, animal studies, EEG, fMRI, MEG, and behavioral measures such as verbal reports and reaction time. No single study settles a hypothesis. Every major claim requires multiple sources of support.

Part of the debate is focused on exactly what it is that is being measured. Every new method of observation is met with that kind of question. The most popular method today is functional magnetic resonance imaging (fMRI). But as we will see, there is ongoing debate about what it is that fMRI measures. The same is true of behavioral measures of working memory, single cell recordings, EEG, and all the rest.

3.5 Major landmarks of the brain

How does brain activity relate to cognition? We will present functional brain images to guide you in interpreting the studies presented in this text. But brain function is always grounded in anatomy, and we will cover the basic geography of the brain for that reason. Figure 1.7 (top) shows the outside view of the left hemisphere, also called the *lateral view*. Below it is the *medial view* of the right hemisphere, also called the *mid sagittal section* of the brain. It is a slice through the midline, from the nose to the back of the head. Every other slice that runs parallel to it is called *sagittal* (see Figure 1.8).

It is important to learn the major landmarks in the brain. Some of the most important ones are the big folds or valleys in the cortex, the outer structure of

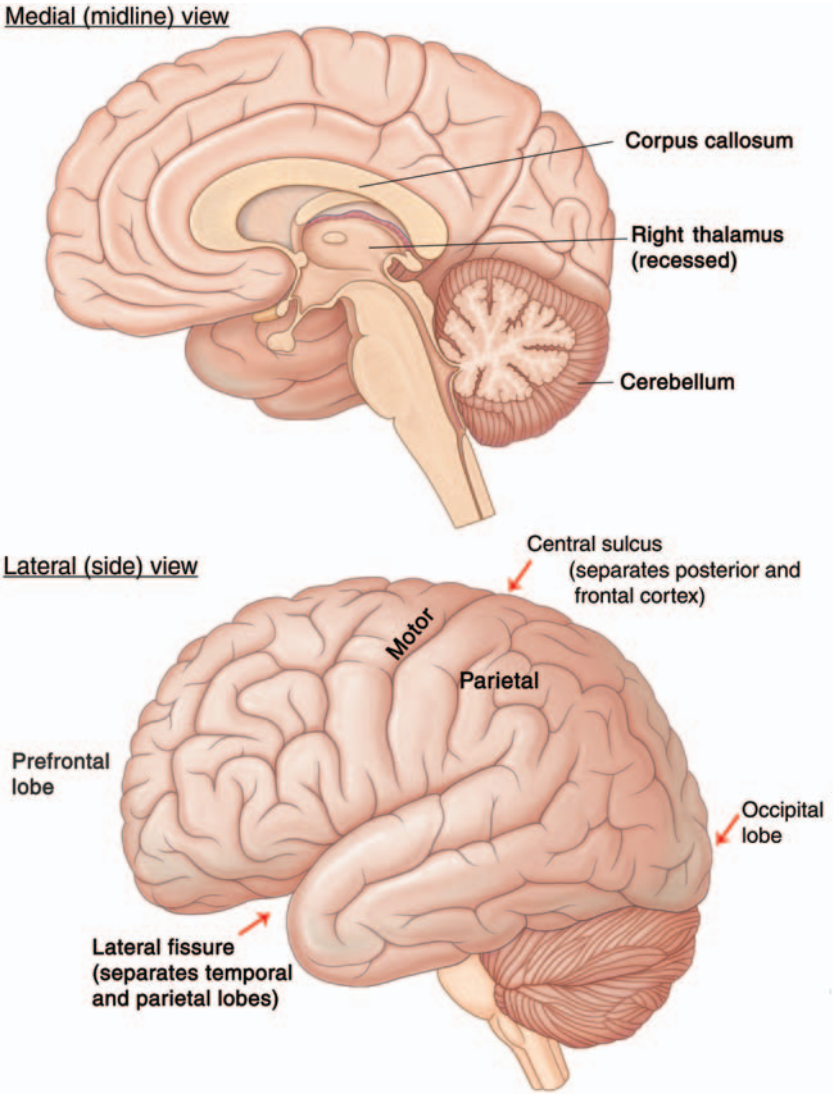


FIGURE 1.7 The brain: medial and lateral views. The top panel shows a medial view of the right hemisphere with major structures highlighted. This view is also called the mid sagittal section of the brain. The lower panel shows a view of the left hemisphere from a lateral (outside) viewpoint. The front of the brain is on the left side of the figure and the back of the brain is on the right side. The four lobes and the cerebellum are labeled. *Source*: Drake *et al.*, 2005.

the brain. The largest valley runs along the midline between the right and left hemispheres and is called the *longitudinal fissure*. A second large fold runs forward at a slant along the side of the brain, and is called the *lateral sulcus* (from the word for the 'ditch' or 'furrow'). The lateral sulcus divides the 'arm' of the temporal lobe from the 'body' of the main cortex. Since the temporal lobe always 'points' in the direction of the eyes, identifying it is the easiest way to tell which way the brain is facing. Spotting the temporal lobe is one of the first things to do when looking at a brain picture.

The *corpus callosum*, another major landmark, is a great fiber bridge flowing between the right and left hemispheres. It is visible on the upper portion of Figure 1.7 as a curved section that begins behind the frontal lobe and loops up and to the back, ending just in front of the cerebellum. When the corpus callosum is cut, it looks white to the naked eye because it consists of white matter (i.e. nerve axons covered by white myelin cells, filled with fat-like lipid molecules). The corpus callosum was called the 'calloused (or tough) body', because that is how it appeared to early anatomists who named these structures. It was discovered early on, because it can be exposed simply by gently separating the two great hemispheres. In Figure 1.9, the corpus callosum is shown beautifully in a classic drawing by the great Renaissance painter Titian, drawn for the first detailed book of anatomy by Andreas Vesalius.

A final landmark is the central sulcus, which divides the rear half of the brain (the posterior half) from the frontal lobe. The posterior cortex is predominantly sensory, with visual, spatial, auditory and body-sense regions, while the frontal lobe is motor and cognitive. The central sulcus is a clear dividing line between the input-and output-related areas of cortex.

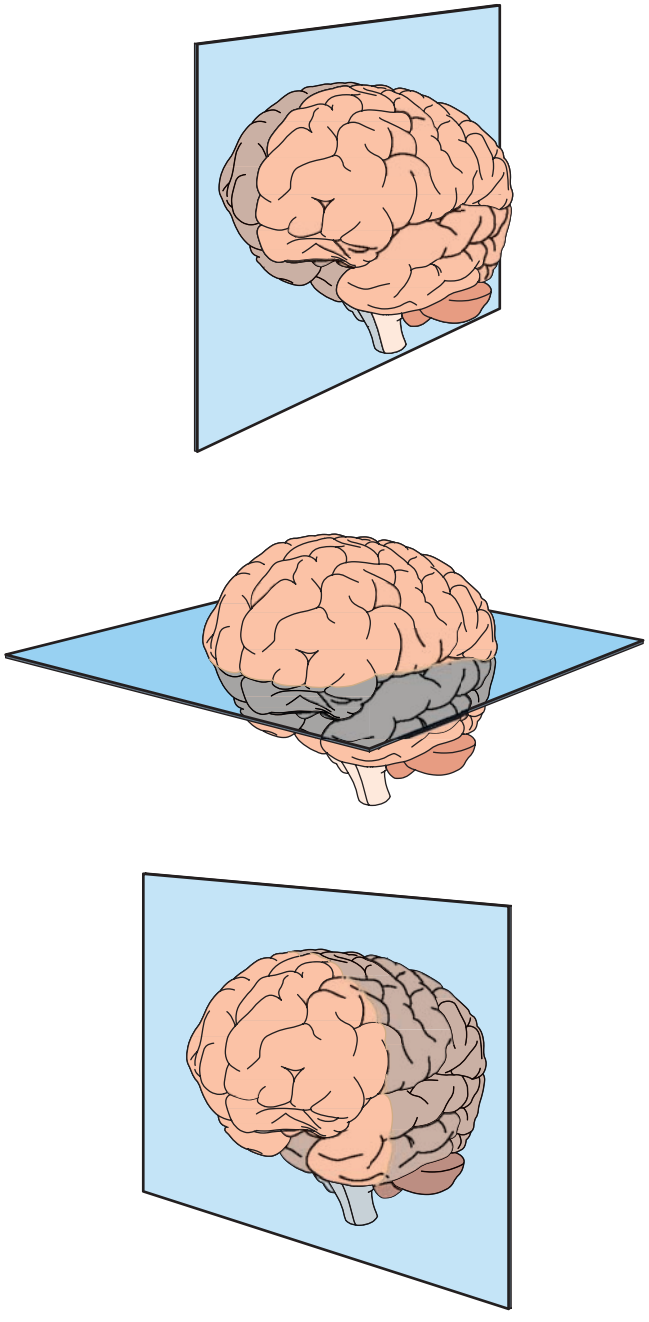


FIGURE 1.8 The major planes of section (cuts). The three main slices or sections of the brain. Top panel shows a vertical section of the brain, called *sagittal*, from the front of the brain to the back. When the slice is exactly through the midline, between the two hemispheres, it is called *mid sagittal*. The center panel shows a *horizontal* slice through the brain. The lower panel shows a *coronal* section (named for its crown shape) like a sliced sausage. (These terms have synonyms that are explained in Chapter 5.)

Locating these three major folds is the first step in orienting yourself.

The cortical lobes flow over to the inside of each half cortex, as we will see. Because it is not easy to understand a knotty three-dimensional object from all perspectives, it helps to hold your own hands in front of you to represent the two hemispheres to remind yourself. It is essential to know the major lobes and other major brain divisions, just as it is to know the names of the continents in earth geography. Throughout this text, we will be presenting brain studies and relating their findings to our understanding of human cognition. These basic brain figures will serve

FIGURE 1.9 *Top*: Andreas Vesalius, showing a dissected arm and hand. Andreas Vesalius was a Belgian physician (1514–1564) who overturned the traditional teaching of anatomy by performing post-mortem dissections of human bodies. He is shown here displaying the exposed hand and arm. The arm and hand were important to Vesalius as evidence for the divine hand in worldly affairs. Until Vesalius, it was widely believed that women had one less rib than men, based on the Biblical story of Adam and Eve. Real dissections of human bodies were not performed, and accurate drawings were rare. Vesalius published his new anatomy, called *On the Fabric of the Human Body* in 1543, the same year as Copernicus' *On the revolution of the celestial spheres*, the revolutionary book about the solar system. Both works became famous and hotly debated. They are milestones in the history of science. *Source*: Masquelet, 1986. *Bottom*: These remarkable ink drawings of the exposed brain are attributed to the great painter Titian, who illustrated Vesalius' classic anatomy, which was a true work of art as well as science. Notice that the two cortical hemispheres on the right have been separated to show the corpus callosum, the great fiber bridge running between the two halves, with some 100 million neuronal axons. To the early anatomists it appeared to be a tough or calloused tissue, and was therefore called the 'calloused body', *corpus callosum* in Latin. *Source*: Squire *et al.*, 2003.

as a guide for interpreting the data of neuroimaging studies that are provided throughout this text.

4.0 SOME HISTORY, AND ONGOING DEBATES

The idea of the brain as the source of our experiences goes back many centuries, as shown by the quotation at the beginning of this chapter (attributed to Hippocrates some 2500 years ago). But careful, cumulative study of the brain really began with the Renaissance. The Antwerp anatomist, Andreas Vesalius, was the first to publish a detailed atlas of the human body, including the brain, in 1543. Before that time, religious and legal prohibitions made it a crime to dissect human cadavers. A century later, a famous Rembrandt painting called 'The Anatomy Lesson of Dr. Tulp' shows the sense of wonder felt by physicians to be able to actually see the human body in detail (see Figure 1.1). Leonardo da Vinci made sketches of the human skull and body at about the same time (1490–1510). The Renaissance was interested in everything human, and the effort to understand the brain grew as part of that broad sense of curiosity.

Today's research is deeply rooted in the history of science. The behavioral sciences date their beginnings to the 19th century. But careful brain studies go to the very beginnings of modern science in the European Renaissance, the time of Galileo, Copernicus, Newton, and Descartes. Color perception really began to be studied with Newton's prism experiments in 1665. The invention of the light microscope by Leeuwenhoek and others in the 1600s leads straight to discoveries about nerve cells and their properties by Santiago Ramon y Cajal in the 19th and 20th centuries.

One pattern in the history of science is that the more we learn, the more we can see simple and general patterns in the evidence. We will bring out these simplifying principles throughout the book.

The Renaissance origins of brain science are clearly apparent even today. Brain terminology is based on Latin, the international language of science for many centuries. We still talk about the *occipital*, *temporal*, *parietal*, and *frontal lobes* of the *cortex*, all Latin words. Because early studies were done with the naked eye or with simple microscopes, most were named for the way they looked visually. Thus, the *thalamus* means the 'bridal chamber', the *amygdala* is the 'almond', *cortex* means 'outer bark', and so on. Practically all brain terms use everyday Latin words. That fact will simplify your understanding of anatomical terms, and we will mention the origins of each term when it is introduced.

The human brain evolved over some 200 million years from early mammalian origins. It is very complex, even the parts that can be seen with the naked eye. Generations of scholars have contributed to its study. For example, Rene Descartes (Figure 1.10) is known today mostly as a mathematician and philosopher. But he was also a careful student of the brain. In one famous observation he obtained the eye of an ox, scraped off the tissue from the back of the eyeball to expose its tough white outer shell, the *sclera*, and showed that light images coming through the lens of the eye were projected onto the white sclera like a screen, so that one could see projected images by pointing the eyeball at a well-lit object. It astonished many people that the visual stimulus was projected *upside-down* on the back of the eye. Descartes was able to show that this is a direct result of the optics of the lens[1].

4.1 The mind and the brain

Descartes is often considered to be the originator of modern mind/body philosophy. The basic question seems simple: is the world basically mental or physical? Or, in today's language, can your conscious experience be explained by neurons? Perhaps nerve cells themselves are just ideas in the minds of scientists. The brain basis of consciousness has now become mainstream in cognitive neuroscience (Edelman, 1989; Palmer, 1999; Koch, 1996; Tulving, 2002; Baars *et al*., 2003a). Numerous articles have appeared in the last fifteen years. In July of 2005, *Science* magazine listed 'the biological basis of consciousness' as one of the top questions in science today. Nobel-winning scientists like Francis Crick, Gerald Edelman and Herbert Simon have devoted years of effort to the question.

In everyday language we constantly switch back and forth between the language of mind and brain. We take a *physical* aspirin for a *mental* headache. We walk to the *physical* refrigerator because we experience a *mental* craving for ice cream. Do conscious experiences 'cause' physical actions, or vice versa? Common sense doesn't care. It just jumps back and forth between the discourse of mind and body. But things get

[1]It still baffles many people that we do not experience the visual world upside-down, since that is how the image is projected on the retina. What do you think is the answer?

FIGURE 1.10 Descartes: philosopher, mathematician, brain explorer. Rene Descartes (left) and his figure showing the optics of the eyes (right). Because Descartes was convinced that the soul or psyche was a unified whole, he rejected the idea that paired structures of the brain could support the soul. But almost all of the brain *looks* doubled to the naked eye: two hemispheres, two eyes and ears, two subcortical halves, and two sides of the cerebellum. Descartes therefore decided that the tiny pineal gland, which looks like a tiny dot to the naked eye, must be the point of connection between the divine soul and the earthly body. Unfortunately for Descartes, microscopic studies after the 17th century showed that the pineal gland also has bilateral symmetry, just like the rest of the brain. *Source*: Bennett, 1999.

complicated when we try to think more carefully. In the physical realm of aspirins and refrigerators, ordinary causality explains how things happen. Ice cream melts in the sun and aspirins dissolve in water. They follow the laws of physics and chemistry. But mental events are affected by *goals*, *emotions*, and *thoughts*, which seem to follow different laws. Ice cream does not melt because it *wants* to – but humans eat ice cream because they want to. Human language has thousands of words to describe desires and experiences, but those words do not apply to physical objects.

As we will see, for the first time, we have a large body of empirical evidence that has a direct bearing on the question of conscious cognition. Some brain regions, like the 'ventral visual stream', are widely believed to support conscious contents, the visual events that people can easily report. There is good evidence, however, that not all brain regions support conscious, reportable events. For example, the dorsal visual stream enables hand-eye coordination in reaching for an object, but there is good evidence that by themselves, these brain areas do not support conscious contents (Goodale *et al*., 1991). Similarly, it is believed that brain regions like the cerebellum do not support conscious experiences. There is growing agreement that the relationship of mind to brain is an empirical, testable question.

4.2 Biology shapes cognition and emotion

Human emotions turn out to have deep biological roots in the mammalian brain, regulated by more recent layers of the neocortex. As a result, the evolutionary history of the human brain, going back some two hundred million years to early mammals, is relevant to a host of important questions. Maternal love and infant attachment now seem to be rooted in an ancient mammalian structure called the peri-aqueductal gray matter or PAG. Vocalizations of distress and

FIGURE 1.11 Charles Darwin and the biology of mind. Many people in the centuries after Rene Descartes were fascinated by the conscious mind and its relation to the brain. Charles Darwin, for example, wrote a book called *The Expression of Emotions in Man and Animals*. Darwin thought about human emotions as biologically based – which was not meant to minimize our vast cultural and individual influences, of course. The picture shows Darwin as a young man, around the time of his historic voyage to the Pacific Ocean on *The Beagle. Source:* Finkelstein, 2000.

attachment seem to have an evolutionary connection to the emergence of speech prosody – the sing-song of language – and even to music. Thus, biology turns out to have relevance in many different ways.

More than anyone else, Charles Darwin helped to establish the biological context of the human species. Darwin made numerous observations about emotional expressions in animals and humans (Figure 1.11). For hundreds of years people must have noticed the similarities, but in Europe and other regions it was essentially taboo to point out those similarities. There is now good evidence about the emotional brain regions that humans share with other mammals (Panksepp, 2005). In Darwin's time that idea was very controversial. Today, Darwin's book *The Expression of Emotions in Animals and Man* is considered a classic (Ekman, 2003).

Darwin would never deny the importance of culture and environment. Humans are the most adaptable species we know, the one most capable of learning new things by way of cultural transmission. The 'nature-nurture' controversy is not really a divisive debate any more. Most scientists see human behavior as combining biology, culture, and environment (see Chapter 15).

FIGURE 1.12 Hermann von Helmholtz was an amateur who ended up making historic contributions to science. Helmholtz was one of the first to propose that the visual system makes 'unconscious inferences' that go far beyond the raw input from the eyes. That idea was so controversial that he was forced to withdraw it, but it is a standard notion in sensory science today. *Source*: Bennett, 1999.

Helmholtz was a great sensory physiologist and psychologist in the 19th century, whose works on vision and audition are still read (Figure 1.12). But his biggest claim to fame is the physical law of conservation of energy, which he demonstrated using electrical stimulation of dissected frog's legs. The insight that electricity was part of nervous activity led to the discovery of nerve potentials and the electrical activity of the brain in the early 20th century. Today, the electromagnetic activity of the brain gives us a whole set of imaging methods: EEG, evoked potentials, single-neuron recording, MEG, and even TMS, magnetic stimulation of the brain (Chapter 4). Indeed, all brain-imaging tools make use of fundamental physics and chemistry.

In Helmholtz' time it was well known that an electrical pulse would cause a pair of frog's legs to contract,

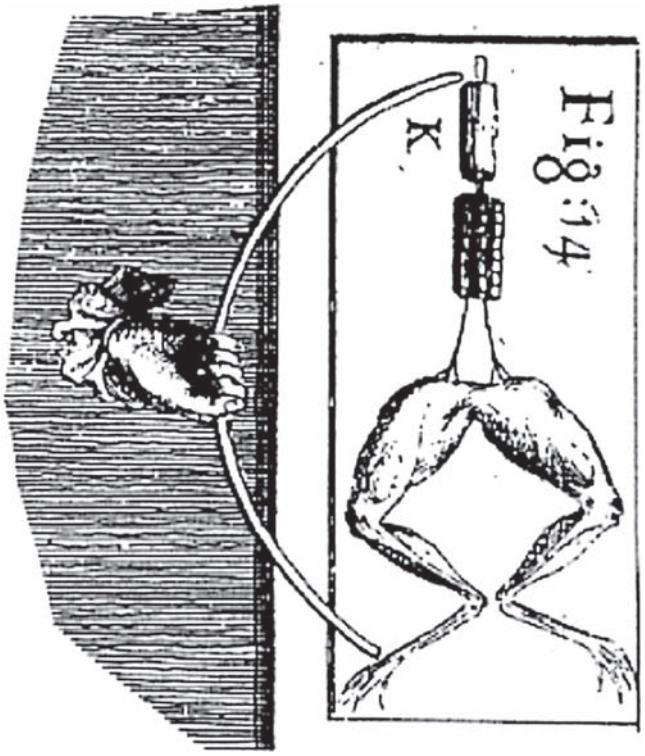


FIGURE 1.13 A schematic of Helmholtz's apparatus for measuring the time course of muscle contraction and the propagation velocity of the nerve impulse. *Source*: Bennett, 1999.

as if the frog were jumping. The idea that the brain and body are pervaded with electricity caught the popular fancy, leading to cult ideas like 'animal magnetism'. Helmholtz' conservation of energy experiment in frogs' legs was a major step towards a naturalistic conception of the brain and body (Figure 1.13).

4.3 Cajal's neuron doctrine: the working assumption of brain science

Santiago Ramon y Cajal (Figure 1.14) is credited with the *neuron doctrine*, one of the founding assumptions of brain science, stating that 'the nervous system consists of numerous nerve units (neurons), anatomically and genetically independent'. It is important to realize that the idea that the body is composed of cells dates back only to 1839, with the use of light microscopes and tissue-staining techniques that showed the details of living cells for the first time in human history.

It became thereby possible to prove that all body tissues consisted of cells, *except* for nervous tissue. The reason was that neurons are immensely branched, and their axons and dendrites spread so thickly, and make such close contact with other nerve cells that it was impossible to tell whether they actually touched or not. Thus a controversy arose over the nature of the

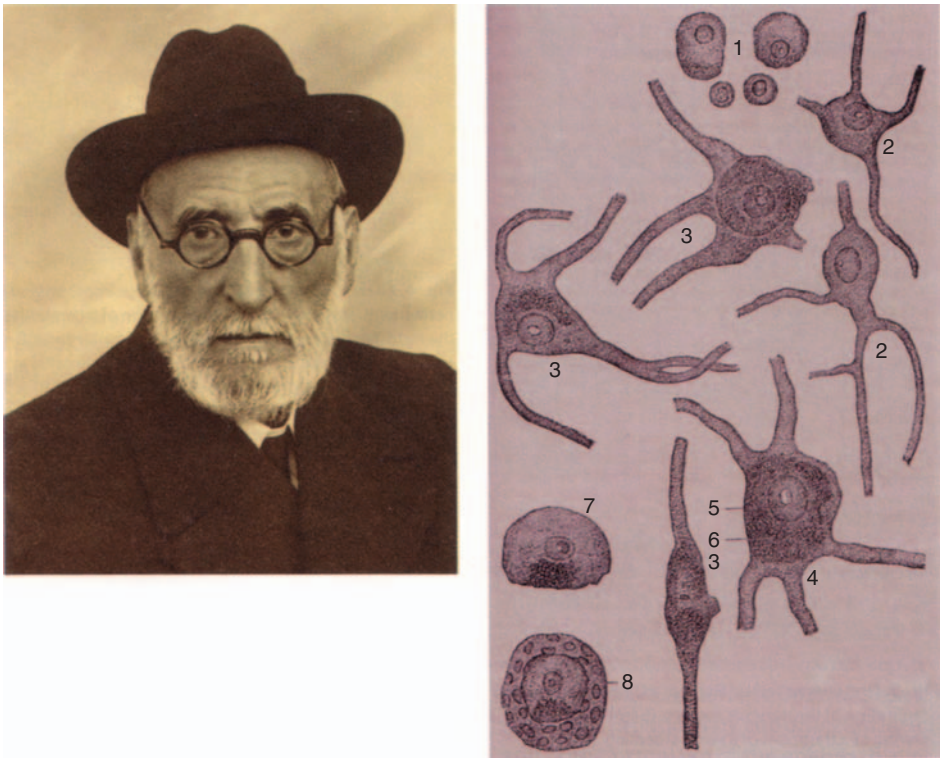


FIGURE 1.14 *Left*: Santiago Ramon y Cajal, founder of brain science. Golgi color stains were used by Santiago Ramon y Cajal, perhaps the most important early pioneer in neuroscience, to bring out basic facts about nerve cells under the light microscope. Cajal showed the microanatomy of neurons. *Right*: His beautiful illustrations of his microscopic observations. Today's methods for studying neuronal microstructure are advanced versions of the Golgi-Cajal approach (see Figure 1.16). *Source*: DeFelipe, 2002.

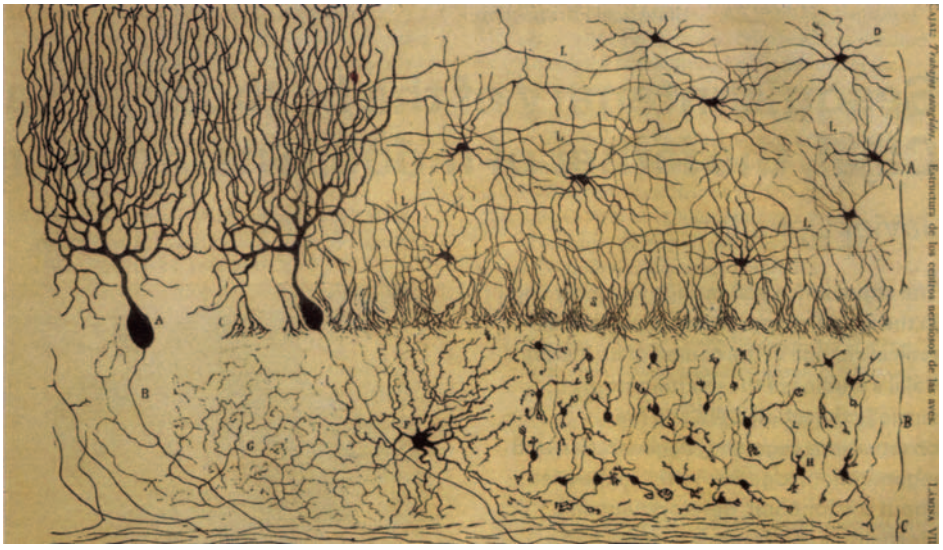


FIGURE 1.15 Cajal's first drawing of a microscopic slice of nerve tissue, from the cerebellum of a hen. Cajal made use of the *Golgi staining method*, which caused small numbers of nerve cells to stand out from the surrounding tissue. *Source*: DeFelipe, 2002.

nervous system – whether it consisted of billions of cells, or whether it was essentially one great continuous network.

In Madrid, Santiago Ramon y Cajal used the Golgi stain, which brought out a small sample of neurons in a slice of tissue in such a way that the shape of the cells could be seen (Figure 1.15). Cajal was also able to prove that axons end in free terminals, and must therefore be separate cells.

The nerve impulse – the electrochemical 'spike' that travels down the axon to its terminals – was first demonstrated in the giant axon of the squid. Because nerve cells are found in all animals, and their basic properties appear to be conserved among many species, the squid axon is an important test-bed for other classes of neurons. That discovery was made in 1939, a century after the cell doctrine was proposed. Ten years later it was found that sodium and potassium ions (Na+ and K+) rapidly move in and out of nerve axons to propagate the axonal spike and, in 1952, Hodgkin and Huxley (1952) constructed the model of the action potential that we use today (Figure 1.16). About the same time, it became possible to observe the even tinier synapse through the use of electron microscopes, down to several hundred micrometers.

There is an ironic ending to the Cajal story, however. The great controversy about whether neurons are separate continues today. Cajal seemed to have settled the question forever when he showed that axons had free nerve endings. However, recent evidence shows that many points of transmission between nerve cells are not chemical synapses but electrically continuous tissue called *gap junctions*. Some neurons are nestled against each other, without the classical synaptic gaps.

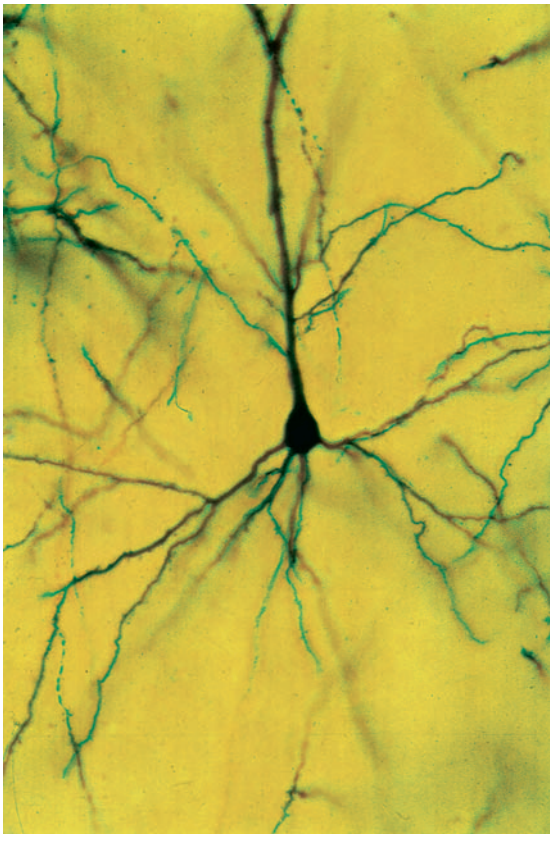


FIGURE 1.16 A modern version of Cajal's figure. Neurons in a modern X-ray micrograph using a chemical stain. *Source*: Standring, 2005.

It is, therefore, possible that some neurons do form a continuous structure, though there is no question that chemical synapses exist in the trillions. Like so many other scientific controversies, the debate goes on at ever more refined levels.

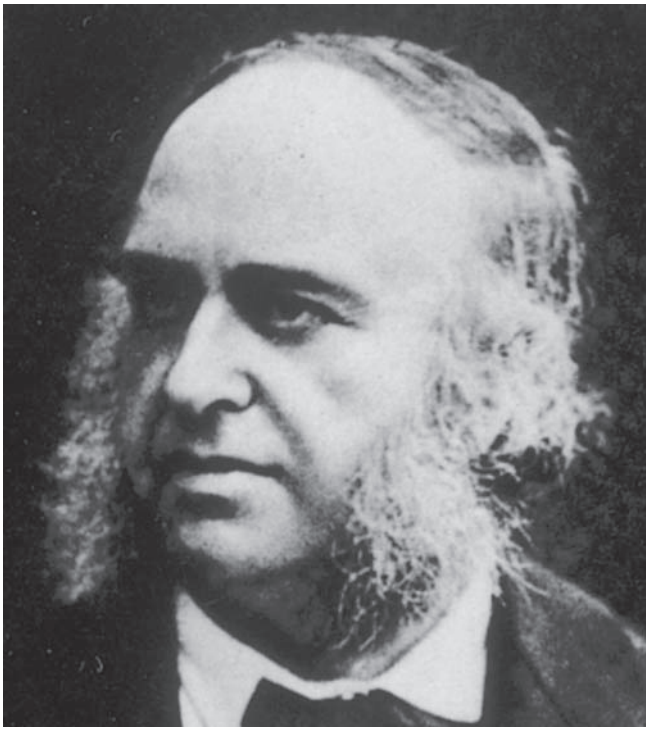


FIGURE 1.17 Pierre-Paul Broca, who defined expressive aphasia. He was the first to make a convincing case for a single, highly specialized function in a specific location in cortex. *Source*: Aminoff and Daroff, 2003.

4.4 Pierre-Paul Broca and the localization of speech production

Medical observations are also relevant to the mind and brain sciences. It was the French physician, Pierre-Paul Broca (Figure 1.17), who first discovered a region of the left hemisphere that was unquestionably tied to language production, a higher mental function. The 'speaking' region of the left hemisphere is therefore called Broca's area.

Controversy has raged over the question of brain localization – whether specific regions of the brain serve very specific functions. Broca was the first to establish firmly a specialized region of the higher brain in 1861, based on a patient who suffered from epilepsy. Broca's patient had lost all ability to speak except the single word 'tan'. After the patient died, Broca was able to perform an autopsy, finding 'damage to the posterior part of the third frontal convolution in the left hemisphere'. The brain of Broca's patient has been preserved and you can see the location of the damage in the frontal region of the left hemisphere. (Figure 1.18). He concluded that this part of the frontal lobe was indispensable for speech production. Six months later, Broca presented a similar case, again with damage to this part of the left frontal lobe. Despite criticisms that

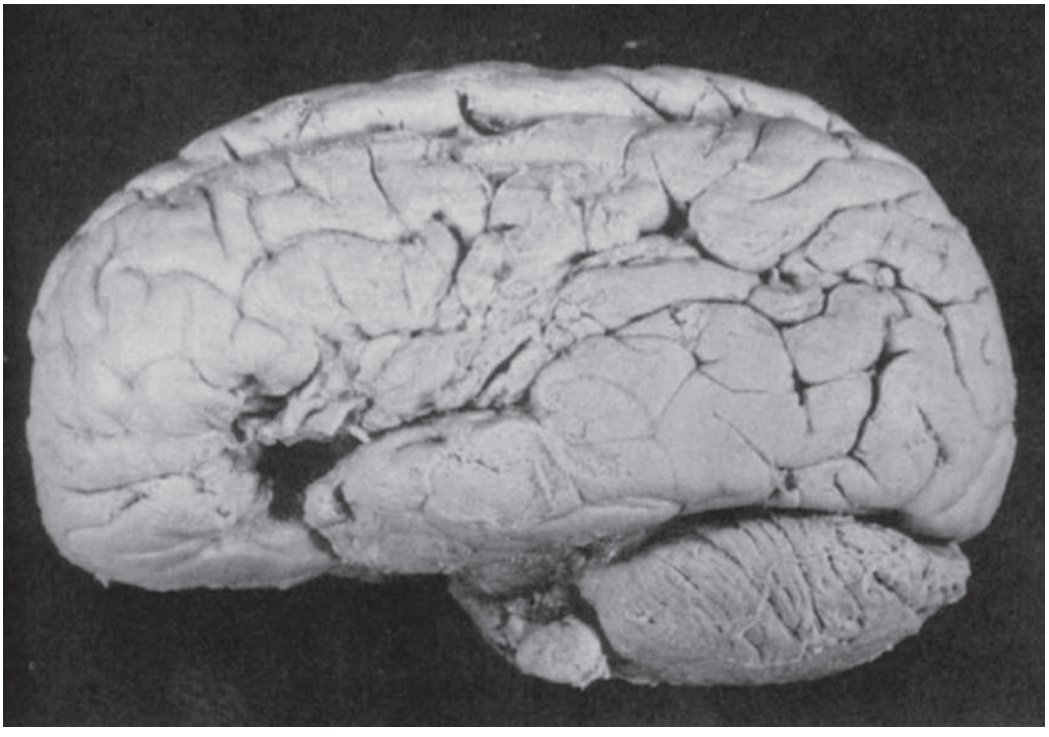


FIGURE 1.18 The brain of Broca's early patient has been preserved. If you look at the frontal region of the left hemisphere you can see a large hole in 'Broca's area'. *Source*: Ramachandran, 2002.

other areas of the brain were involved in his cases and that some patients with similar disorders did not have frontal lobe lesions, Broca's observations came to be accepted because of the weight of subsequent evidence. Today, Broca's area in the left frontal lobe is widely recognized as a critical component of the language region (Aminoff and Daroff, 2003).

Much of what we know about the human brain was first discovered from very careful study of specific deficits. That effort continues today. Another important finding for language was made by Carl Wernicke (Figure 1.19), who published a monograph in 1874 describing a model for language based on his work in human pathology that remains a key aspect of cognitive neuroscience today. Today, Wernicke's area in the left upper part of the temporal lobe is widely recognized as an important brain area for receptive language. Patients with brain damage in this region and deficits in speech comprehension are still called 'Wernicke's aphasics'. However, with better techniques of brain imaging, these areas are turning out to be more complex and flexible than they were thought to be.

Here is a speech sample from a modern patient (FL) with receptive aphasia, due to damage in or near Wernicke's area (Dronkers and Ogar, 2003):

Examiner: Tell me what you think your problem is.
FL: Ah, where do I start the tesseinemen from? They tell me that my brain, physically, my brain is perfect, the attitudes and everything is fine, but the silence now, that I have to reeh-learn through edgit again, physically nothing wrong with it. It's perfect the doctors tell me. They have attitude. Physically I have loozing absolute nothing on my head, but now I have to go through these new attitudes to looalize how, some, how can I say to? Some what that I can reeh-learn again so I can estep my knowledges, so th'you kyou again, what how can I say that y . . .

Notice that this patient is much more fluent than Broca's classic patient of 1861 who could only pronounce one syllable. However, this patient's ability both to produce and comprehend meaningful speech is impaired. Using brain imaging, the location of focal damage is routinely determined today so that diagnosis is no longer dependent only on neurological inferences and autopsies.

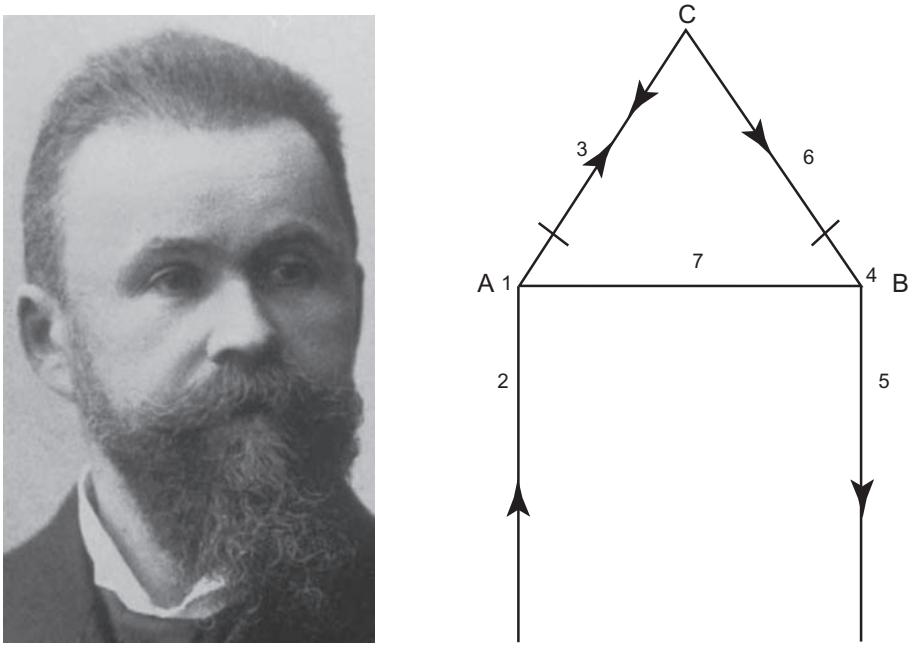


FIGURE 1.19 Wernicke and the comprehension of speech. Some years after Broca's work on speech *output*, the German physician Carl Wernicke (left panel) discovered a part of the brain involved in speech *input* – perception and comprehension. Wernicke studied a variety of aphasic patients (a-phasia, meaning 'not speech'), and concluded that damage in different cortical locations led to different disorders. He distinguished between *semantic* aphasias and *receptive* and *productive* types. The right panel shows the 'house' model (because it looks like a simple drawing of a house) for language areas from the 19th century. The label A refers to the auditory language area for comprehending speech, B refers to motor language area for producing speech, and C refers to the distributed representations of concepts throughout the brain. *Source*: Wernicke and Koehler, 2003.

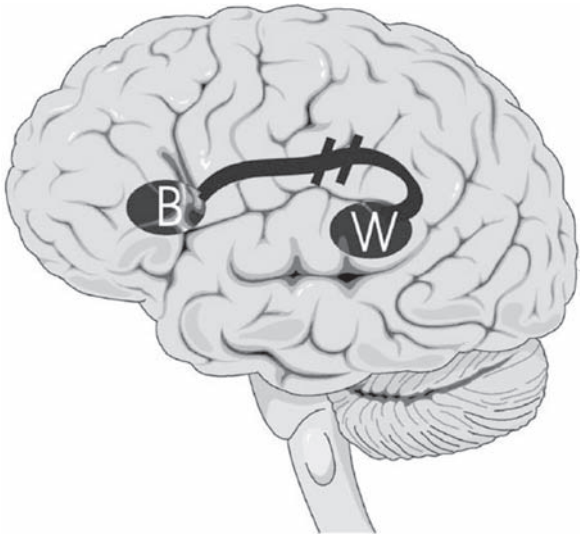


FIGURE 1.20 Conduction aphasia. Careful anatomical dissections showed a fiber bundle connecting Broca's and Wernicke's areas of the left hemisphere. Based on this evidence, Wernicke was able to predict a new language deficit in 1874 called *disconnection aphasia.* If the fiber bundle between Broca's and Wernicke's areas were damaged, he thought, patients should have difficulty transferring information from the receptive area to the production region. That prediction was borne out and this type of deficit is called conduction aphasia. *Source*: Dronkers and Ogar, 2003.

It was well known in the 19th century that most of the mass of the cortex is *white matter*, consisting of billions of axons emerging from the gray cell bodies in the surface layers of the cortex. Those axons are wrapped in the white protective and supportive myelin cells, filled with fat-like lipid molecules. They therefore look white to the naked eye. Most of the white matter therefore consists of great fiber bundles, connecting every region of cortex to every other, like some great highway system. Careful anatomical dissections showed a fiber bundle connecting Broca's and Wernicke's areas in the left hemisphere. These fiber bundles are known as *arcuate fasciculi*, Latin for 'arched little bundles'. (Again, an everyday Latin term has become a long and complicated-sounding word to our ears.)

Based on this evidence, Wernicke was able to predict a new language deficit in 1874 called *disconnection aphasia*. If the fibers between Broca's and Wernicke's areas were damaged, he thought, patients should have difficulty *repeating* speech sounds – transferring information from the receptive area (Wernicke's) to the production region (Broca's). That prediction was borne out (see Figure 1.20). It is believed that there are a number of such disconnection syndromes, with somewhat different symptoms from lesions that involve damage to the outer cell bodies of cortex. A number of other types of aphasia are thought to exist.

Notice that these language areas usually exist in the left hemisphere (Figure 1.21). Modern evidence shows that the right side of the brain does comprehend language, but it does not control vocal output. The right side is believed to be sensitive to the emotional content of language, such as humor and irony. Left-side dominance seems to apply to about 90 per cent of the population. About 10 per cent of normal people have right hemisphere dominance for language.

William James (Figure 1.22) is best known today as a psychologist and philosopher, however, he also trained to be a physician and painter. James was first hired at Harvard University to teach brain anatomy, and his 1890 description of the brain is in good agreement with our understanding today. Note his drawing showed Broca's and Wernicke's areas based on the medical evidence from aphasias (Figure 1.23).

James' *Principles of Psychology* is often considered the best summary of 19th century psychology and brain science in the English language. Among many other points, James discussed the brain studies of a Dr. Mosso, who observed that the blood supply to active brain regions increased (Figure 1.24). That finding is the basis of modern brain imaging methods based on *hemody-namics* (the flow of blood), including PET scans and MRI (Figure 1.25).

> [In Mosso's experiments] the subject to be observed lay on a delicately balanced table which could tip downward either at the head or at the foot if the weight of either end were increased. The moment emotional or intellectual activity began in the subject, down went the balance at the head-end, in consequence of the redistribution of blood in his system. (William James, *Principles of Psychology* (1890))

Thus, 19th century scientists discovered localized brain functions for language. They were not only concerned with the classic psychological aspects of the mind, but also with their relation to the brain.

4.5 The conscious and unconscious mind

Nineteenth century physicians believed that human conscious experience depended on the cortex, the outer layer of the brain. James wrote:

> But is the consciousness which accompanies the activity of the cortex the only consciousness that man has? or are his lower centres conscious as well?. . . the cortex is the sole organ of consciousness in man.

Contemporary neuroimaging evidence tends to support James' claim, although some scientists believe that subcortical regions are also involved (see Chapters 2 and 8). The question of conscious perception

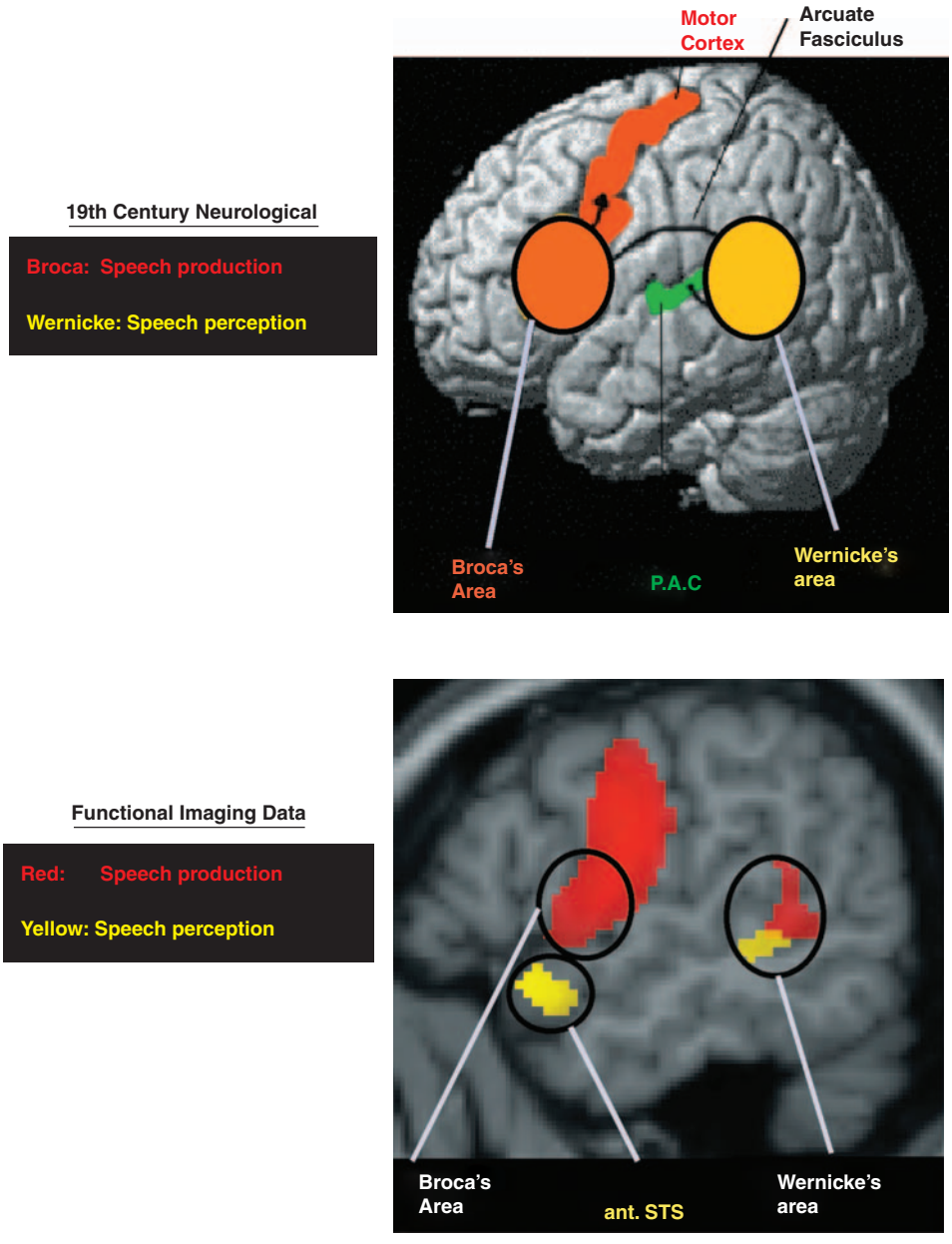


FIGURE 1.21 Language regions of the left hemisphere, studied by fMRI (functional magnetic resonance imaging). Red areas are involved in speech *production*, while yellow ones show up in speech *perception* and *comprehension*. The classic Broca's and Wernicke's areas are marked by circles. Notice the close similarity between the modern understanding of language regions and the 19th century account. (PAC = Primary Auditory Cortex, the initial region in the cortex for second processing; ant. STS = anterior superior temporal sulcus, the front part of the upper fold of the temporal lobe.) *Source*: Frackowiak, 2004.

and cognition has again become a major focus of research, as we will see.

Nineteenth century scientists were profoundly interested in the question of consciousness. Ramon y Cajal proposed the idea of a 'psychic neuron' in the cortex, a type of neuron that would support conscious experiences. The beginning of psychophysics in the early 19th century was very much inspired by an effort to solve the mind-body puzzle, and the pioneering psychophysicist, Gustav Fechner, claimed that he had found the answer by showing a mathematically exact relationship between subjective sensory intensity and physical stimulus intensity. At the end of the 19th century, William James proclaimed that 'Psychology is the science of mental life', by which he meant *conscious* mental life (James, 1890/1983, p. 15). James was not alone.

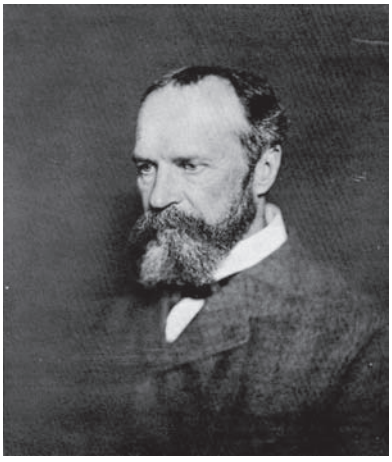


FIGURE 1.22 William James taught brain anatomy. While William James is best known today as a psychologist and philosopher, he also trained to be a physician and artist. James was first hired at Harvard University to teach brain anatomy and his 1890 description of the brain is in good agreement with our understanding today. *Source*: Courtesy of the National Library of Medicine.

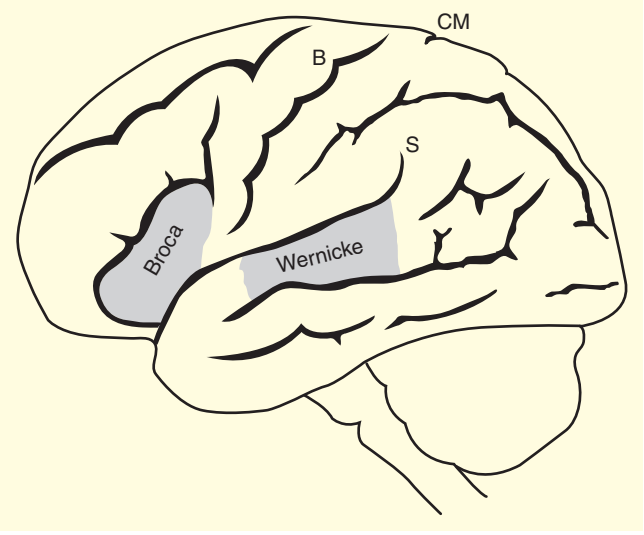


FIGURE 1.23 James showed Broca's and Wernicke's areas based on the medical evidence from brain damage. *Source*: James, 1890.

About that time, some began to disagree. Scientists like Helmholtz, Loeb, and Pavlov advocated a more physicalistic view of mental life. After 1900, Pavlov became famous for his experiments on classical conditioning in dogs. This helped to convince many psychologists that ultimately all behavior could be explained in terms of simple behavioral units, based on reflexes (Figure 1.26). In the USA, John B. Watson was the first person to make radical behaviorism famous, arguing that any reference to consciousness was improper, since we can only publicly observe physical behavior and the physical brain. Watson's famous slogan was

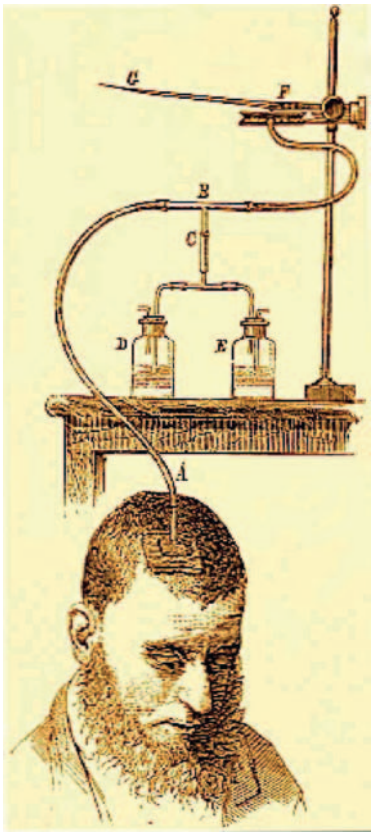


FIGURE 1.24 William James (1890) described the research of Dr. Mosso, who found a way to measure blood pressure during demanding mental tasks. Mosso's work anticipated current measures of brain blood flow like fMRI. *Source*: James, 1890.

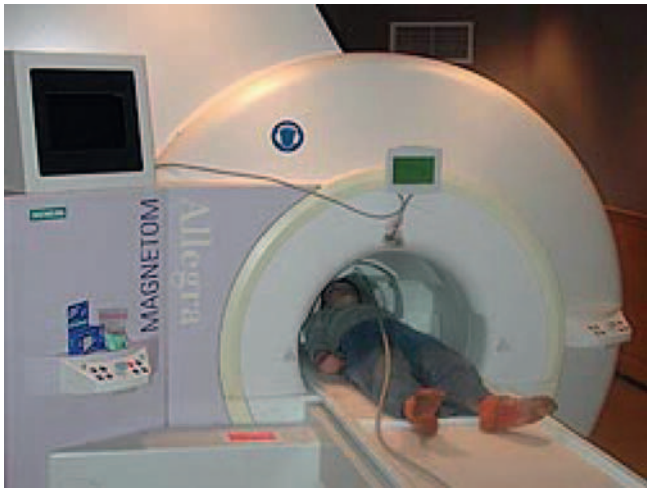


FIGURE 1.25 Functional MRI measures local blood flow changes in the brain. Contemporary fMRI experiments are based on blood flow changes in the brain whenever some brain regions require more oxygen and glucose. It is a modern version of Dr. Mosso's 19th century discovery. *Source*: Thomas Ramsøy.

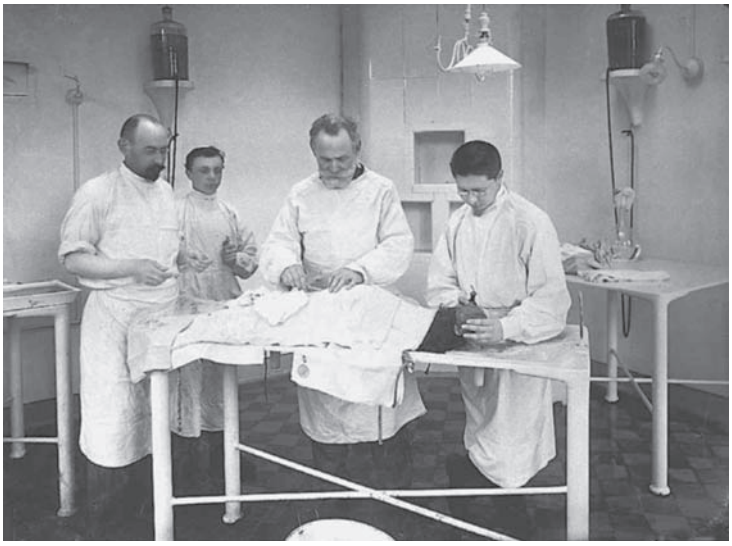


FIGURE 1.26 Pavlov operating with three colleagues on an anaesthetised dog in the department of Physiology, Imperial Institute for Experimental Medicine, St. Petersburg, c. 1902. *Source*: Tansey, 2006.

that 'consciousness is nothing but the soul of theology', and therefore unscientific. For much of the 20th century human consciousness was avoided by scientists. Some saw it as too burdened with philosophical questions, too difficult to test experimentally or too subjective to be studied scientifically.

There were some practical reasons for this. It is difficult in many cases to be sure about someone else's experience, so that it can be hard to repeat experiments in the way reliable science requires.

FRONTIERS OF COGNITIVE NEUROSCIENCE

A biological theory of consciousness

FIGURE 1.27 Gerald M. Edelman, MD, PhD, The Neurosciences Institute, San Diego, CA, USA.

We all experience a stream of conscious experiences — our inner speech, thoughts and feelings, our sense of who we are. Conscious knowledge of ourselves and the world emerges in the first few years of life. It is something we share with millions of others, yet it is very private: no one else sees, feels, or understands our personal conscious viewpoint exactly as we do. Awareness is omnipresent in humans and yet intimate and personal. At the same time we know there are regions of the brain, like the cerebellum, that do not give rise to conscious experiences. So what is the difference between brain regions that result in conscious reports and those that do not? (Chapter 8)

The brain bases of consciousness is a core topic of the mind–brain sciences. A leader in this quest is Dr. Gerald Edelman, Nobel Laureate and Director of the Neurosciences Institute, and Chair of the Department of Neurobiology at the Scripps Research Institute in La Jolla, California. Edelman also has a lifelong professional interest in classical music and performance. Gerald Edelman has developed a biological theory of brain function called Neural Darwinism, with a central role for conscious contents, which continues to be developed (see Chapter 8).

Neural Darwinism is a large-scale theory of brain development and function. It suggests that brain development and brain dynamics are *selectionist* in nature, not

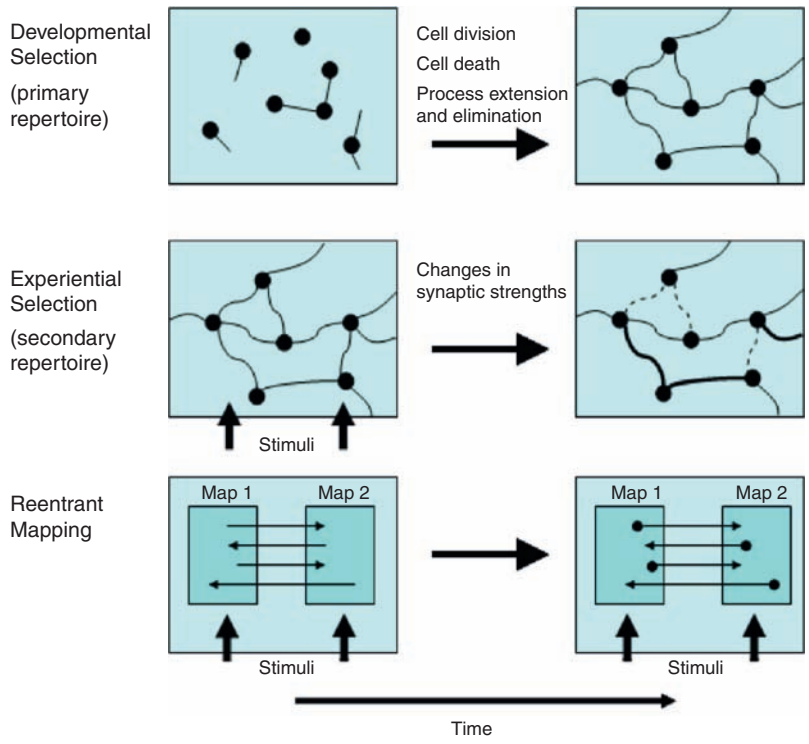


FIGURE 1.28 The three main tenets of Neural Darwinism. Developmental selection yields a diverse set of neural circuits by cell division, cell death, and the extension of neuronal branches, the dendrites and axons, to reach out to others and build synaptic connections. In the next stage, experiential selection leads to changes in synaptic strengths favoring some pathways over others. Reentrant connections enable coordination of neural activity between different regions of the brain. (Black dots indicate strengthened synapses.) *Source*: Squire, 2004.

instructionist, as in the case for digital computers, which carry out explicit symbolic instructions (see Figure 1.28).

Selectionist systems have four features:

1. A set of elements that are characterized by *diversity*, like the members of a species, antibodies in the immune system, or neurons in the brain.
2. These elements can *reproduce* or *amplify*.
3. A process of *selection* operates on the products of diversity. In evolution, selection favors some offspring in the species and not others. In the immune system, selection operates on successful antigen–antibody matches. The brain has two selectional repertoires, one developmental, with the *neurogenesis* of a vast body of neurons, and a *connectional* repertoire as neurons make synaptic connections and prune all but the successful ones to produce the mature brain. The repertoire of connections continues to adapt and grow throughout our lives.
4. Finally, selectionist systems show *degeneracy*, the ability to use different combinations of elements to perform the same function (Edelman & Gally, 2001). Degeneracy applies to all levels of life. We have two lungs, two halves of the brain, and a great many redundant pathways at all levels of biological organization. Degeneracy makes it possible to overcome damage and disease by using alternative pathways and organs. It can enable living things to survive setbacks.

Conscious experiences

According to Edelman, conscious experiences result from reentrant interactions among neurons in the thalamocortical system, the core of the mammalian brain. **Reentry** is the constant resonant activity between two ensembles of neurons, which serves to modify the connections between them, and also to select the members of the ensembles themselves. It is a highly adaptive process, comparable to social networking, where the networks continue to expand and develop depending on person-to-person interactions. In this view, a subset

of thalamocortical neurons work together in a large "dynamic core" of interacting neurons. The dynamic core as a whole can change from moment to moment, to adapt to new conditions, retrieved memories, and goals. Primary consciousness concerns the perceptual world as well as memory; higher-order consciousness extends beyond primary consciousness to language, abstraction, and thought.

One property of consciousness is its extraordinary range of contents — sensory perception, visual imagery, emotional feelings, inner speech, abstract concepts, and action-related ideas, to name only some. The broad range of contents reflects the fact that consciousness involves multiple brain regions. Sensory cortex clearly contributes to conscious perceptual events, but there is evidence that nonsensory regions like the frontal and parietal cortex are involved even in sensory experiences, like the sight of a coffee cup. An integrative view of consciousness must also include interactions among brain regions involved in conscious recall, conscious control of motor skills, and the like. Edelman and colleagues have suggested that the workings of the dynamic core could handle such a wide range of brain activities.

This broad outline has been filled in by biologically anchored modeling of the thalamocortical system, the hippocampus, and other regions. Some of these models run robots in realistic environments, to see if they can learn in ways that resemble mammalian learning.

Edelman and Tononi (2000; Tononi & Edelman, 1998) suggest that the content of any conscious event is not simply a consequence of activity in the relevant cortical area. The sensation of redness does not come from activity in the visual cortex alone, although such activity may be required. Rather, a sensation of redness is determined by the state of the entire dynamic core. More formally, any conscious event can be represented by a single point in an N-dimensional space, where N represents the number of neuronal groups that are part of the dynamic core at any time. A sensation of redness is therefore entailed by a very high dimensional discrimination — not just a discrimination among possible colors, but rather occurs among a vastly larger number of possible dynamic core states.

According to the extended theory of Neural Darwinism, the diversity of conscious contents arises from the ways in which different neuronal groups influence the N-dimensional space. Although a large proportion of the mammalian cortex is surprisingly uniform in its histology, input to different cortical areas varies greatly. For example, visual input is very different in its statistical structure from proprioceptive input. Neuronal groups sensitive to color may therefore organize the space in a way different from those sensitive to proprioception. Each sensory modality will therefore influence the state of a dynamic core in a unique manner, and this may explain why the content of a conscious event dominated by vision is reliably different from one dominated by a sound, a touch, or a taste.

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5.0 THE RETURN OF CONSCIOUSNESS IN THE SCIENCES

In the 1970s, many psychologists became dissatisfied with behaviorism and began to pursue a different path. While using behavioral measures in the laboratory, cognitive psychologists were interested in making inferences from those observations. We will see one prominent example in this chapter, the idea of working memory. There are many others. Cognitive psychologists have brought back visual imagery, various types of memory, unconscious (implicit) cognition, and many other terms. However, these concepts are always studied behaviorally in the laboratory under very closely controlled conditions. The concepts of working memory, imagery, and so on, are inferred from behavioral observations. They are theoretical explanations, much as electrons are in physics. No one has ever seen an electron, but the concept of an

BOX 1.2 The mind-brain debate today

Philosophers continue to debate whether conscious experiences can be understood in terms of the brain. However, many scientists today believe that it has become a productive scientific question again. Patricia Churchland has been among the leading philosophers coming back to a naturalistic approach to the mind and brain. She recently said that 'neuroscientific data are relevant to longstanding, traditional problems in philosophy: the nature of consciousness, the self, free will, knowledge, ethics and learning'.

Psychologists have studied sensory processes since the early 1800s. We experience our world through our senses: we have the feeling that our mind-brain is intricately involved with the interplay between our physical world and our brain. We readily get help for our perceptual abilities by obtaining eyeglasses from optometrists, hearing aids from audiologists. And we spend time tuning the objects that provide us with some of our sensory inputs, such as car speakers and audio equipment. Yet the correspondence between our visual and auditory perception of the world and the physical properties of that world is still not entirely known. Clearly, the mind and brain have a sense of sights and sounds within our environment, yet mapping the path between the physical and the perceived remains a mystery.

It seems that words like 'mind' and 'brain' represent different *sources* of information. If we look out at the world from within our brains (as we are always doing), things seem different than if we look at our brains from the outside, in a brain scanner, for example.

When a computer shows us how much memory it has, no one thinks that it has just discovered a new realm of existence. When people tell us about their sensory experiences, they have not done so either. But they have told us something valuable. Philosophical journals are still filled with mind/body debates, but scientists must define questions in empirical terms. Today, we are increasingly confident about the evidence from both mental and brain perspectives, and we are beginning to see how the two points of view converge when we study them carefully.

FIGURE 1.29 Patricia Churchland has been among the leading philosophers coming back to a naturalistic approach to the mind and brain. *Source*: Patricia Churchland, UCSD.

electron explains many different kinds of observable phenomena (Baars, 1986).

> Perhaps the greatest change over the last twenty years within cognitive psychology and cognitive science more generally, has been the acceptance of consciousness as a legitimate and tractable scientific problem. During much of the twentieth century the field was enmeshed in the philosophical tangles of the body-mind problem, and stifled by the empirical limitations of introspectionism. More recently, it has gradually become clear that neither of these represent the sort of fundamental obstacle that was originally feared. Furthermore, the need to account for phenomena such as blindsight and implicit memory, in which perception and recall were clearly proceeding in ways that were at variance with the conscious experience of the perceiver or the rememberer, argued strongly for the need to bring back the study of conscious awareness into the empirical psychological fold. (Baddeley, personal communication)

In recent years, the reluctance to study consciousness has begun to fade. Many cognitive psychologists study both explicit (conscious) and implicit (unconscious) processes. As we will see, there is now a large body of evidence that our perception of the world around us is partly unconscious, although the *result* of the perceptual process is conscious. Many aspects of memory are unconscious, while episodic memory involves the record of conscious events in the past. With the advent of functional imaging technology, it has become possible to make careful comparisons between brain events involving conscious versus unconscious cognition. Currently, about 5000 articles per year refer to consciousness and its many synonyms. The synonyms include 'awareness', 'explicit cognition', 'episodic recall', and 'focal attention'. Those terms are defined experimentally by measures of 'accurate report'. We simply ask people if they perceived or recalled an event, and then try to check the accuracy of their reports. In that sense, the different synonyms

TABLE 1.3 Commonly studied conscious and unconscious brain events

Conscious	Unconscious
1 Explicit cognition	Implicit cognition
2 Immediate memory	Longer term memory
3 Novel informative and significant events	Routine, predictable and non-significant events
4 Attended information	Unattended information
5 Focal contents	Fringe contents (e.g. familiarity)
6 Declarative memory (facts etc.)	Procedural memory (skills etc.)
7 Supraliminal stimulation	Subliminal stimulation
8 Effortful tasks	Spontaneous/automatic tasks
9 Remembering (recall)	Knowing (recognition)
10 Available memories	Unavailable memories
11 Strategic control	Automatic control
12 Grammatical strings	Implicit underlying grammars
13 Intact reticular formation and bilateral intralaminar thalamic nuclei	Lessened reticular formation or bilateral intralaminar nuclei
14 Rehearsed items in working memory	Unrehearsed items
15 Wakefulness and dreams (cortical arousal)	Deep sleep, coma, sedation (cortical slow waves)
16 Explicit inferences	Automatic inferences
17 Episodic memory (autobiographical)	Semantic memory (conceptual knowledge)
18 Automatic memory	Noetic memory
19 Intentional learning	Incidental learning
20 Normal vision	Blindsight (cortical blindness)

for conscious events are assessed in the same way, and therefore seem to have a basic similarity. We will call them 'conscious', but also use the technical terms (see Baars *et al*., 2003).

In the 19th century, figures like Sigmund Freud and William James were deeply interested in understanding the relationship between mind and brain. Freud began his medical career in neurology, and even developed an early neural network model. Early in his career he discovered a new chemical stain – gold chloride – which allowed certain neurons to stand out clearly under the microscope. The first such stain was discovered by Camillo Golgi in 1873, and revolutionized the ability to observe nerve cells under the light microscope (see http://nobelprize.org/medicine/articles/golgi/).

5.1 How conscious and unconscious brain events are studied today

Psychologists and neuroscientists have devised a very wide range of methods for studying conscious and unconscious processes in the brain. Table 1.3 shows a subset of all the methods currently available. They all have pros and cons, of course. Some have implications for episodic memory (memory for conscious events), while others show that visually guided reaching for objects is largely unconscious. There are many unresolved questions, whether 'conscious' cognition is the best terminology, whether selective attention must precede conscious experiences, and much more. All these debates are healthy and normal. The most important advance is that we now have a number of reliable methods for studying both conscious and unconscious brain events (Figure 1.30). We can contrast brain activation patterns for imagined versus actual events, as well as for stimuli that are not consciously perceived (see Table 1.3).

The most important point is that, from a scientific point of view, conscious cognition is much like working memory or attention. It is a *construct inferred from behavioral observations* (Mandler, 2003). Fortunately, it also corresponds usually to our own personal experience.

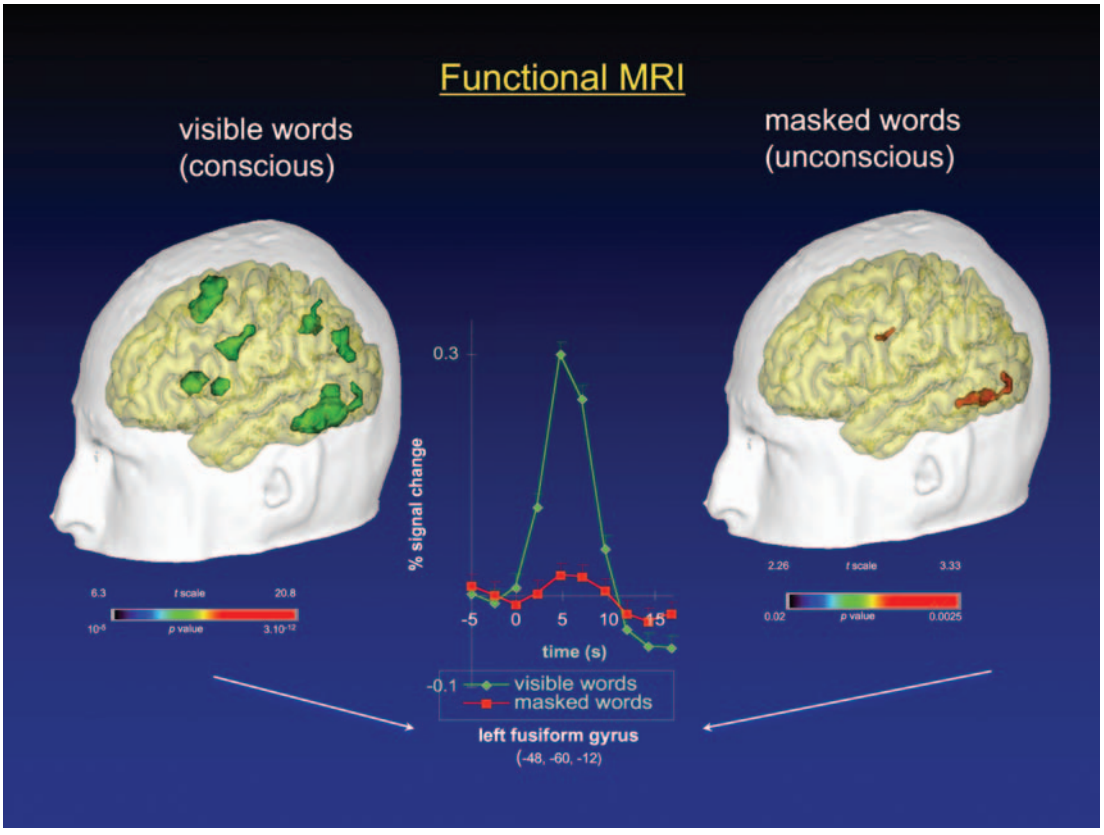


FIGURE 1.30 Unconscious versus conscious vision. A recent wave of experiments compares conscious and unconscious phenomena in the same study. For example, a method called visual backward masking allows us to compare fMRI activity in the same person for conscious and unconscious visual words. This figure from Dehaene *et al.*, 2001 shows that unconscious words trigger local activity in visual cortex, but matched conscious words *also* evoke strong forward activity in the cortex, in the parietal and frontal lobes. In both experimental conditions the same physical stimulus reaches the retina, so that the difference must be higher up in the brain. This pattern of results has now been found a number of times. Evidence like this has convinced a number of scientists that conscious cognition can be studied with the proper kinds of experimental designs. *Source*: Baars *et al.*, 2003.

In the study of perception, for example, you can report the type-face of *these words*, or even your memory of this morning's breakfast. This topic has been emerging in a number of fields within cognitive neuroscience such as memory, vision, and lesion studies, as we will see in later chapters.

5.2 History hasn't stopped

Practically all the historical debates are still alive today, often appearing in a new guise (see Table 1.4). The practical applications of cognitive neuroscience continue to grow. Modern neurology makes extensive use of brain imaging and cognitive techniques to assess subtle kinds of damage that are not visible in scans. New research has shown unsuspected deficits, for example, such as emotional blindness and the inability to use certain nouns and verbs. These subtle signs can point to serious brain damage that is not otherwise detectable.

TABLE 1.4 Ongoing debates today

Local versus widespread functions in the brain
The neuron doctrine
The question of consciousness
Unconscious inferences in vision
Capacity limits in the brain
Short-term and long-term memory: are they separate?
The biological bases of emotions
Nature *versus* nurture, genes *versus* environment

6.0 SUMMARY

In this first chapter, we explored some of the questions we try to understand in cognitive neuroscience. They encompass some ancient issues such as the mind versus the body, as well as some that arise from very recent experiments. The scientific exploration of the relationship between the mind and the brain is a central issue addressed by this text. The advent of imaging techniques has brought many of these questions back to life.

Cognitive neuroscience combines psychology, neuroscience, and biology. The historical roots of the discipline go back to some of the earliest writings in Eastern and Western traditions. Questions that were out of bounds a few years ago are now being explored. For students, new careers are opening up. Practical applications are emerging in education, medicine, and psychotherapy. Major challenges remain, but there is a sense of excitement in the air. New findings are coming faster than ever before.

The goal of this chapter has been to give you an overview of the combined study of mind and brain. We now have brain imaging studies of vision and hearing, learning and memory, conscious and unconscious processes, visual imagery and inner speech. This is an extraordinary time in science. Most imaging experiments use standard cognitive tasks, so there is a growing integration of the behavioral and brain evidence. The implications for brain functioning in health and disease are immense.

The field of cognitive neuroscience aims to make sense of the flow of new evidence. This chapter presented a first broad overview. Our goal is to show you how mind and brain evidence often fit together in a surprising and satisfying way.

BOX 1.3 Adaptation or representation?

There is another debate that continues today: should brains be viewed as adaptive or representational? This debate concerns how we think about cognitive processes and the way in which to map them onto brain systems. Here is some background.

As you read this sentence, you are engaging in a *symbolic interpretation* of a string of black squiggles on a colored background. Linguists and psychologists think about language in terms of symbols: phonemes, letters, morphemes, words, phrases, and sentences. Those symbolic units are combined by the regularities of grammar and usage. Educated speakers of English understand about 100,000 words, often with more than one meaning – roughly the number of words in a good dictionary. At a higher level, we think in terms of sentences that encode abstract concepts and propositions, and these can be combined into even larger-scale discourse structures, like expository paragraphs, conversations, and stories. Even the expressive function of language – the emotional singsong of a phrase, or a verbal statement of anger or love – can be described symbolically: human languages have many words for emotions. In sum, we are remarkably skilled in the use of symbols. They are essential in cultural developments like science, mathematics, and logic, but also in literature, music, and the visual arts. Even computer programs are symbolic systems that perform useful work. Symbols are all around us, and it is therefore natural to think about the brain as a symbolic processor.

Yet the physical brain only contains neurons, connected to each other in a variety of ways. Should we think about the mind-brain as a symbol processor, or as a hypercomplex web of neurons? Each approach has pros and cons. Symbols allow us to explore questions of meaning and purpose fairly easily. Symbolic flow diagrams, like the 'functional framework' of Chapter 2, help to clarify questions that can be tested in the laboratory.

On the other hand, artificial neuronal network models (ANNs) can simulate simple learning tasks better than symbolic systems (see Chapter 2). We therefore have a range of tools – flow diagrams, artificial neural networks, semantic networks, tree diagrams, and models – that combine symbols and neurons. In fact, if you look closely, even neural networks have nodes and connections with symbolic names.

Scientists are constantly debating these questions. Cognitive neuroscience is a discipline in ferment, with waves of new evidence and theory constantly challenging our ability to understand. It is an exciting and fun enterprise, and we hope that in the coming chapters you will catch a glimpse of what keeps us fascinated with a flow of new insights into human minds and brains.

BOX 1.4 How to study in this course

We highly recommend drawing and coloring as a way of learning the geography of the brain. As you know, learning requires active involvement. That is especially true in a course like this. There is no substitute for careful reading, thinking, asking questions, and exploring answers. It can be helpful to study with another person who is also focused on learning. But because the brain is a 'hypercomplex surface', drawing is especially valuable. Most chapters in this book will present drawing and coloring exercises at the end.

The traditional way to learn the brain is by dissecting sheep and frogs. That is effective because the student is constantly interacting with the physical brain. We will ask you to study this text and its graphics just as if it were a living brain, but without having to harm any creature. Our figures are designed to show the many levels of anatomy and to illustrate the most important experiments.

Because the brain is a vast, three-dimensional structure squeezed over millions of years of evolution into a very small space, learning its ins and outs is much like getting to know a city, to drive or walk around it, to memorize the major landmarks, and to visit some of the back alleys and individual houses. This book will be your tour guide, pointing out landmarks and the customs of the inhabitants.

For major learning points in the text there will be a demonstration, a graphic image, or experimental evidence. In the coming chapters we will see case histories of people who have suffered brain injuries, and explore some of the limits of normal brains as well.

Finally, it is important to break down the technical terms into their parts. Anatomical studies of the brain began four centuries ago, when the international language of science was Latin. Many brain terms are therefore still compounds of Latin and Greek. For that reason it is important to recognize *cognates* – words that are similar to English. For example, in this chapter we saw the cortex from one side (the *lateral* view), from the midline (the *medial* view), the bottom (*inferior* view) and the top (*superior* view). Those four words – *lateral, medial, inferior* and *superior* – have obvious English analogs. Fortunately, much of our English vocabulary comes from Latin-based languages, so that you will often be able to spot connections with familiar words.

It will help you to do *elaborative learning*, rather than just repeating new words to yourself. The top of the brain is often called the dorsal part, because *dorsum* means 'back' in Latin, and if you look at dogs or cats walking, the top of their brain is an extension of their backs. As we just mentioned, the side is called lateral; therefore structures that are on top *and* to the side are called *dorsolateral*. We will explain those subunits as each new word is introduced.

Anatomy students often use memory techniques. You may want to explore them to see which ones work best for you. Medical students traditionally draw the brain and color its parts. But any kind of active association will help – rhyming the words, making up visual images, or thinking of analogies. You might visualize the brain as an automobile, and associate different brain structures with the tires or the hood. Don't worry if the associations seem silly, so long as you get a clear mental connection between what you are learning and what you already know. Just as there are no bad questions, there are no silly memory techniques. Just ones that work for you, or don't.

Finally, *self-testing* is an essential ingredient of learning, just as it is for playing an instrument. Otherwise we tend to overestimate what we know. Remember that just being able to *recognize* a word does not mean that you'll be able to *recall* it when you need it. If you expect a recall test, it helps to practice recall.

It may help you to browse the web for different ways of looking at cognitive experiments and brain images. If you feel ambitious, the National Library of Medicine has a free web database with tens of millions of scientific abstracts. *PubMed* will answer all kinds of scientific and medical questions (search for *Entrez PubMed*). There are outstanding brain anatomy sites, and many excellent websites that demonstrate basic cognitive and perceptual phenomena.

7.0 END OF CHAPTER EXERCISES

7.1 Study questions

1 Name three small-scale spatial events in the brain, with their order of magnitude.
2 Name three small-scale temporal events in the brain, with their order of magnitude.
3 What was the dominant viewpoint about the nature of psychology in the 19th century? In the early 20th?
4 What is a major difference between behavioral and cognitive psychology?
5 What influence did physiologists like Pavlov have on psychology?
6 Explain some ways in which psychology and brain science interact.
7 What are some difficulties in studying brain damage scientifically?
8 What is the relationship between the 'mental' point of view and 'physical' perspective? What is philosophical naturalism?
9 In everyday life, are you aware of using inner speech? Visual imagery? If so, in what situations? If not, what everyday situations might show that kind of process? (Note that there are considerable

(*Continued*)

individual differences in visual imagery; not everybody reports having spontaneous images.)

7.2 Drawing exercise

We highly recommend drawing and coloring to help you remember the physical layout of the brain.

Here is a model brain for your use. It is very helpful to draw or color the following areas. Many people find it useful to make a habit of coloring brain parts in consistent colors, to help to associate brain regions by color. All kinds of memory aids can help.

1. The major lobes (seen from the outside view, both right and left).
2. What are the names of the major lobes?
3. Where is Broca's area? Wernicke's? What are their traditional functions?
4. What anatomical structure connects these two areas?
5. Draw the brain from the left side, labeling the major lobes.
6. Which area is associated with vision? With speech? With executive control?

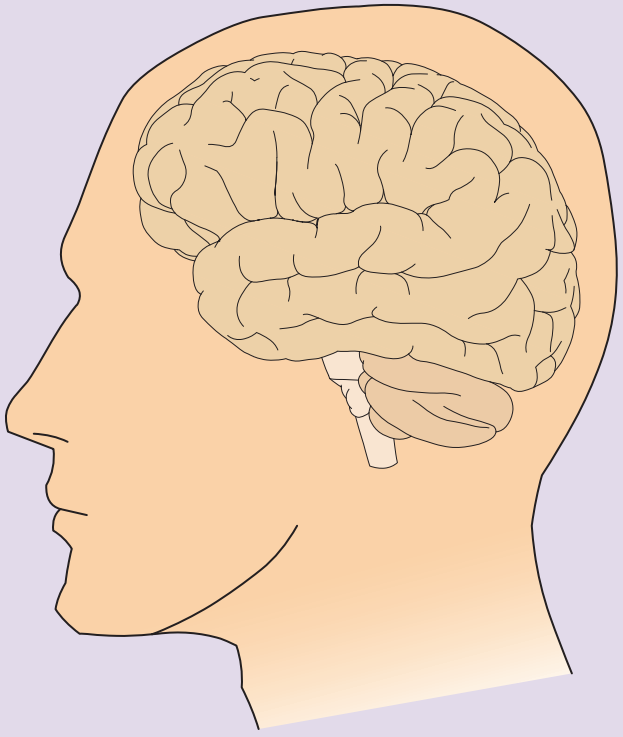
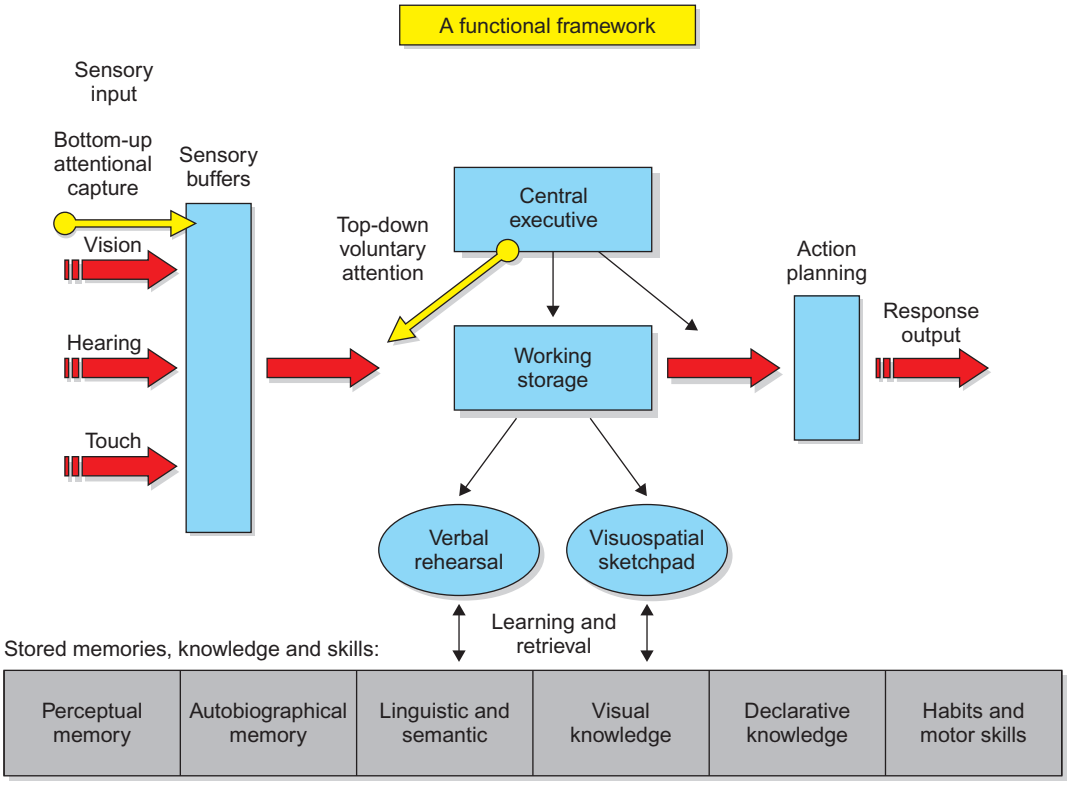


FIGURE 1.31

It seems that the human mind has first to construct forms independently before we can find them in things. . . . Knowledge cannot spring from experience alone, but only from a comparison of the inventions of the intellect with observed fact.

Albert Einstein (1949)



This functional framework, used throughout this book, combines two classical models of cognition (Baddeley and Hitch, 1974; Atkinson and Shiffrin, 1968). Two yellow arrows symbolize voluntary (top-down) and spontaneous (bottom-up) attention. Long-term memories, knowledge, and skills are shown in the row of gray boxes at the bottom. In Chapter 8 we add 'conscious cognition' for reportable brain events, such as your conscious perception of the page in front of you (Baddeley, 2002). While the diagram is only an outline, it has the advantage of simplicity and wide acceptance. It should be taken as a first sketch of mind and brain functions. A recent version of Baddeley's Working Memory model is shown in the center.

CHAPTER

2

A framework

OUTLINE

1.0 INTRODUCTION

In this chapter, we introduce a framework that will help to organize a good deal of cognitive neuroscience. While not all of the details are settled, it combines a large body of brain and psychological evidence into a single diagram. Because cognitive neuroscience can be complicated, an organizing framework will help you learn.

The figure on page 32 shows our framework schematically, and Figure 2.1 shows some associated regions of the cortex. As we will see, there is both behavioral and brain evidence for all the components. But we will hold this organization lightly, as just one way to understand the evidence. When there are debates about how to interpret the facts, we will explore their pros and cons.

In this chapter, we will briefly touch on each aspect of the functional framework. Each 'box' is expanded in later chapters.

The left side of the figure on page 32 begins with the sensory systems. The senses all begin from receptor

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

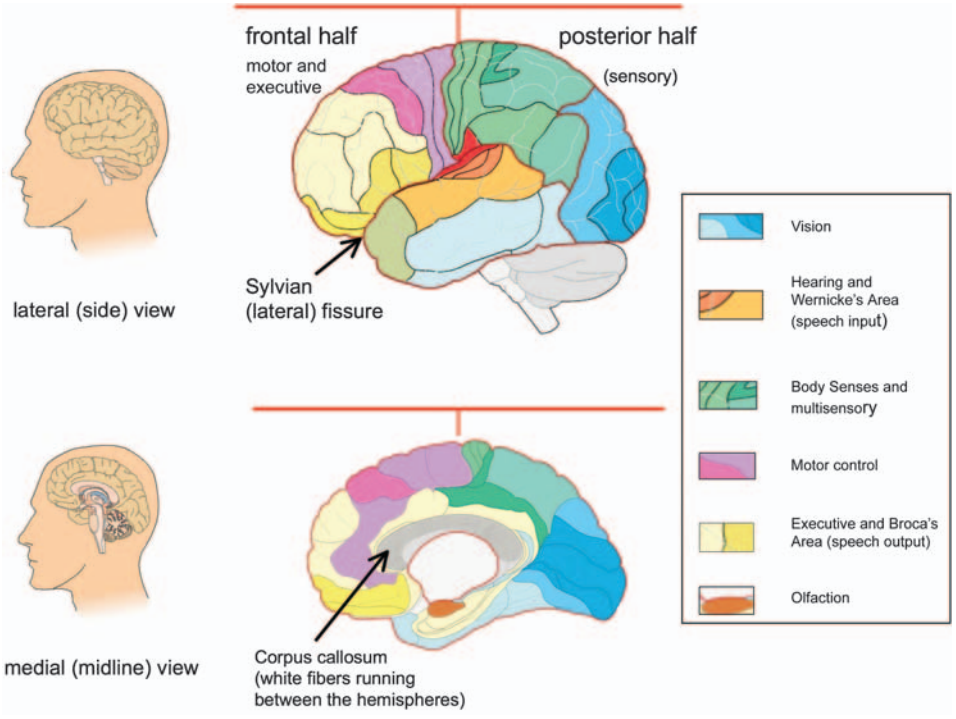


FIGURE 2.1 Some major functions of the human cortex. The lateral (side) and medial (midline) views of cortex are colored to show major functional regions. The colored regions should be memorized to make it easier to understand the rest of the book. On the right of both figures are the sensory halves of cortex, the posterior cortex, including the occipital cortex for vision and part of the upper temporal cortex for hearing. The body senses are represented just behind the central sulcus (light green). On the left side of the central sulcus are motor regions (light purple), and in front of the motor cortex, the prefrontal cortex for executive functions. Thus we can conveniently divide the cortex into input regions in the posterior half and output regions in the front half, at least as a first approximation. (This figure does not show subcortical regions or input-output pathways.) (See Chapter 5.) *Source*: Drawn by Shawn Fu.

surfaces containing millions of receptors, like the retina at the back of the eye. All sensory pathways terminate in the rear half of the cortex, as shown in Figure 2.1. Each of the classical senses is believed to have a brief storage ability called a *sensory buffer*. Vision and audition have been studied for more than two centuries and a great deal is known about them. The body senses, like touch, pain and proprioception, are also well understood. However, even though the smell and touch senses were the earliest to evolve, they are not as well understood as the others. New sensory abilities are still being discovered, including those involved in circadian rhythms, digestion, and even for sexual and reproductive functions.

Sensory activities are flexibly enhanced by *selective attention*, shown by the two yellow arrows in the figure on page 32. As the diagram shows, attention has a 'bottom-up' component, to reflect the times when our sensory experience is captured by a flash or a bang, or more subtly by the sight of someone's face. We can also pay attention to a range of events voluntarily in a 'top-down' fashion. That is how we normally call each other's attention to something interesting. While there continues to be debate about brain regions involved in selective attention, recent evidence shows that cortical regions for visual attention show marked overlap with eye movement control (see Chapter 8).

While this diagram has no symbol for conscious experience, we will see in Chapter 8 that there is an intimate relationship between selective attention and perceptual consciousness.

2.0 CLASSICAL WORKING MEMORY

In the middle column of boxes in the figure on page 32, we have the classical components of working memory (Baddeley and Hitch, 1974; Baddeley, 2002). These components have been studied in great depth over three decades.

Starting from the top, working memory includes the *central executive*, which is the subject of much current research. The central executive was first studied in learning

tasks. However, as the frontal lobes have become better understood, executive functions have expanded to include supervisory control over all voluntary activities (e.g. Luria, 1976, Goldberg, 2001; see Chapters 8 and 11). It is often described by the metaphor of a chief executive officer of an organization. For example, Mateer *et al*. write:

> Imagine the role of the executive of a large company, who has overriding control over the company's actions. This person sets goals, plans and organizes company activity to meet those goals, and decides when to start to do something, when to stop doing it, when to do something else, and when to do nothing at all.
>
> The executive is *future directed* and *goal oriented* and, to be effective, must be *flexible* and adaptive. At a basic level, this is what the prefrontal cortex does for humans. (Mateer *et al*., 2005; italics added)

The word 'prefrontal' means the forward part of the frontal lobes. The prefrontal executive regions are located in front of the purple motor regions of the brain (see Figure 2.1). They are marked in light beige and yellow colors, on both the outside and inside views of the hemispheres. Notice that Broca's area, first discovered in the 19th century, is technically a part of the prefrontal cortex. However, the light purple motor regions (on both sides of each hemisphere) also have some executive functions, though typically more local ones compared to the classical prefrontal cortex. These boundaries are not absolute, but they are convenient as a first approximation. Later chapters explore executive functions in more detail (see Chapter 12).

Just below the central executive box in the figure on page 32, the diagram shows a *working storage* element. In the brain, working storage is believed to involve the medial temporal cortex and prefrontal regions. Working storage is dynamic – i.e. it involves active populations of neurons called *cell assemblies*, which can 'crystallize' into permanent memories. Because working storage is dynamic, it is more vulnerable to disruption than are permanent memories.

2.1 The 'inner senses'

Another step down in the diagram are two of the 'inner senses', labeled *verbal rehearsal* and the *visuospatial sketchpad*. Notice that they interact constantly with the gray boxes along the bottom, the long-term stores. Verbal rehearsal is now thought to be another term for inner speech, the fact that human beings seem to spend most of their waking hours talking to themselves (Luria, 1976; Morin, 1993). Inner speech is not just for rehearsing and memorizing information; rather, it keeps a running commentary on our 'current concerns', while the vocal tract is inhibited, so that we do not express our inner speech out loud (Singer, 1993). Because it involves the sophisticated human language capacity, inner speech is closely tied to the *linguistic and semantic* component of the long-term stores, shown at the bottom of the diagram.

It is easy to demonstrate basic features of verbal rehearsal by means of immediate memory tasks, like trying to remember a telephone number or a shopping list. In the brain, Broca's and Wernicke's areas are involved in inner speech, as you might expect from Chapter 1 (see the bright yellow and orange regions in Figure 2.1). However, language-related areas extend far beyond the traditional Broca-Wernicke cortex. As we will see, semantics, the representation of abstract concepts, also engages temporal and frontal lobes.

The visuospatial sketchpad refers to our ability temporarily to hold visual and spatial information, such as the location of a parked car, or the route from home to a grocery store. Visual imagery is easy to demonstrate, for example by asking people to visualize their front door, and then asking them on which side the doorknob is located. Even people who do not consider themselves to be vivid imagers usually report 'seeing' their doorknob on the right or left side of their imagined front door. Kosslyn and others have found many brain and behavioral similarities between visual imagery and visual perception (e.g. Kozhevnikov *et al*., 2005). In general, these authors believe that visual imagery makes use of a subset of visual perception areas. Thus the blue areas of the brain figures might participate in visual imagery.

However, the visuospatial sketchpad also involves more abstract and *cross-modal* (involving more than one sense or 'mode') spatial information. For example, we can close our eyes and identify objects by touch, even though we may never have touched them before. There must therefore be cross-modal transfer between vision and touch. Such cross-modal flow of information is associated with parietal cortex (shown in green in Figure 2.1), sometimes called the 'Where stream' as opposed to the 'What stream' of the lower visual areas. The auditory sense also has a spatial component – we can locate sounds quite accurately with our eyes closed, especially if they have fast, high-pitched transients, like the chirps of a sparrow. Thus, all the sensory systems begin as domain-specific visual, auditory, or touch perception, but are quickly interpreted as part of a common multimodal space that surrounds our bodies.

The visuospatial sketchpad and the verbal rehearsal component of the functional framework involve mental capacities that we use to remember new words, new faces, spatial information, such as whether to turn

right at a specific street corner, and so on. These everyday capacities have an evolutionary basis in language and the spatial senses. It seems likely that there are also 'inner senses' involved with smell and taste, body sensations, pain and pleasure, and the like. It has been shown, for example, that expected pain activates brain regions that overlap with those that become active for real pain. However, it is the verbal and visuospatial 'inner senses' that have been studied the most. We will focus on them.

Long-term stores are represented by the horizontal row of boxes along the bottom of the figure on page 32. These are the brain stores for autobiographical episodes, various kinds of knowledge, and practiced expertise. Once these memory types are stored, they are not conscious. However, they interact constantly with active functions.

All parts of the system work with the others – and they may occasionally compete against some of them as well. For example, visual and auditory stimuli tend to compete if they cannot be integrated into a unified experience. A good example is a movie in which the sound and visual tracks are out of sync. When they are desynchronized by more than about one-tenth of a second, they tend to interfere with each other. When they are synchronized, they tend to unite perceptually (McGurk and MacDonald, 1976). We perceive the speech as coming from the person whose mouth is moving in just the right way at the same moment.

2.2 Output functions

On the right hand side of our diagram are the output components. These include the *central executive*, *action planning*, and *motor output*. The best example here is voluntary motor functions, notably the ones that control our skeletal muscles – the muscles of the torso, head, and face. We have no voluntary control over the smooth muscle systems of digestion and blood flow, or over the vital hormonal system. Because these physiological systems have long been known to be autonomous from voluntary control, they were called the *autonomic nervous system*. The autonomic nervous system is anatomically separate from the voluntary motor system, which is under frontal control.

Humans also have voluntary control over some mental functions. A good example is verbal rehearsal and mental rotation of a visual image. If you can visualize a kitchen chair, you may be able to rotate it upside-down mentally. This kind of imagery task activates motor, spatial (parietal) and visual cortex. Because it is voluntary, it is presumably controlled by prefrontal regions.

To see how the functional framework can be used, we will consider a tragic type of brain damage, the case of a man who lost his ability to translate his moment-to-moment experiences into lasting memories.

2.3 Only a fleeting moment . . .

One day in 1985, a rising young musician in Britain realized that he could not remember his wife's name. That same evening, Clive Wearing tried to remember the names of his two children and failed (Figure 2.2).

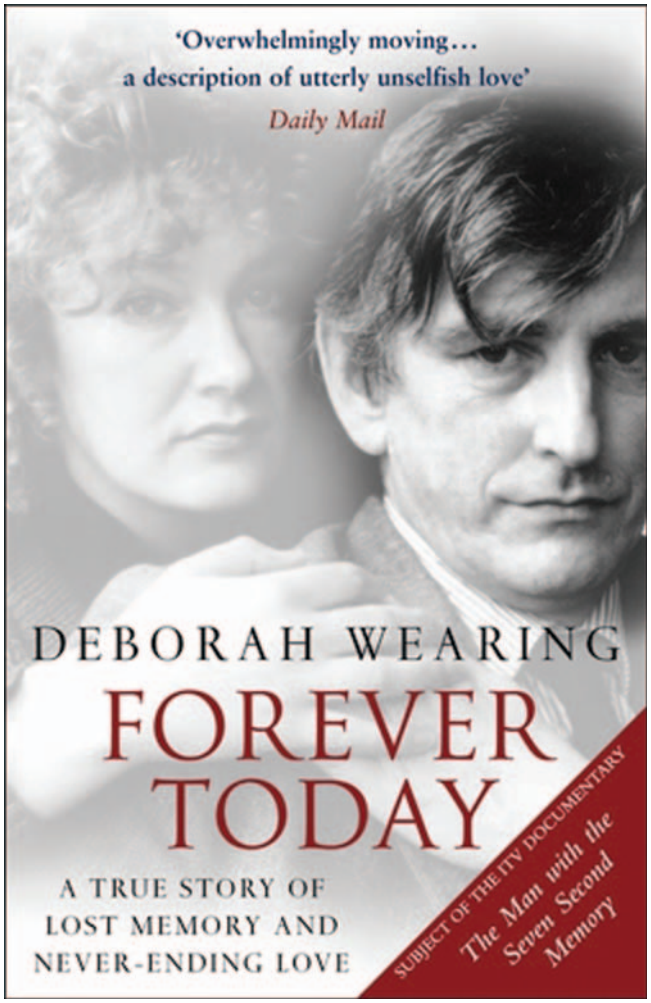


FIGURE 2.2 Clive Wearing (with his wife Deborah Wearing) on the cover of Deborah Wearing's book. After losing both hippocampi (plus some damage to frontal regions), Clive Wearing was still able to play piano and conduct musical pieces that he knew before the injury. However, he could not learn new episodic (conscious) events. Wearing could retain conscious experiences for perhaps ten or twenty seconds, suggesting that aspects of his immediate memory were intact. However, he was catastrophically impaired for episodic learning, i.e. for transferring conscious information into long-term episodic memory. *Source*: Wearing, 2005.

Deborah and Clive Wearing had been married shortly before the onset of his condition, but he could not recollect the wedding. His condition, which was permanent, came on without warning after two days of severe headaches and fever. That was long enough for a viral infection to destroy regions in Clive Wearing's brain that are needed for new memories to form. Wearing was stricken with chronic, dense amnesia of unusual severity, including both *episodic* memory loss – he could not remember any past experiences – as well as a partial loss of *semantic* memory – an inability to understand some domains of meaning (Wilson *et al.*, 1995). Most crucially, he was unable to learn new information. His life, as his wife Deborah later said, was suddenly narrowed to 'a single, blinkered moment', without past or future.

Clive Wearing has been the subject of twenty years of news stories, studies, and television documentaries. His case is particularly dramatic because he seems unchanged as a person. He is fully conscious of the immediate world around him, can read and write, and can carry on a conversation in the present moment. Wearing can even conduct his small chorus in a classical music piece, provided he already knows the music. He is an emotionally intense person, perhaps even more than before his injury, particularly in expressing his feelings for his wife Deborah.

Clive Wearing lives in an eternal present. For the first eight years, he spent every day in his hospital room writing in his diary, trying to recapture what he called his consciousness. Every few minutes he wrote down the time of day, followed by the exclamation, 'I am now conscious for the first time!!' A few minutes later, he would cross out the previous entry, believing that he had not really been conscious at all, because he could not recall that moment. The same routine was repeated thousands of times, filling numerous diaries. But when his wife or friends came to visit, he greeted them as if he had never seen them before: they were familiar, but not identifiable. If they left for a few moments, Clive Wearing could no longer remember their visit. Even today, whenever Clive Wearing sees his wife Deborah he believes he has not seen her for a long time. Read more about the story of Clive and Deborah in Deborah's own words (Wearing, 2005).

We know more about Clive Wearing's personal life than about others with similar damage. However, by far the most scientific studies have been conducted with a patient we know only as HM, who was first studied by Brenda Milner and Herbert Scoville (Scoville and Milner, 1957). In the 1950s, there were few drug treatments for epileptic seizures. A treatment of last resort for severe, untreatable epilepsy was the surgical removal of part of the temporal lobe. In the case of HM, the two hippocampi and some surrounding regions in the middle temporal lobes were removed on both sides (Figure 2.3). Careful studies over decades showed that HM was unable to store new autobiographical episodes – defined as memories of his conscious life experiences. However, HM was able to learn new sensorimotor skills, called procedural memories. Like Clive Wearing, HM's ability to understand the meaning of language and of basic events was largely spared. Thus, his *semantic memory* – his ability to understand the meaning of things – was not seriously impaired.

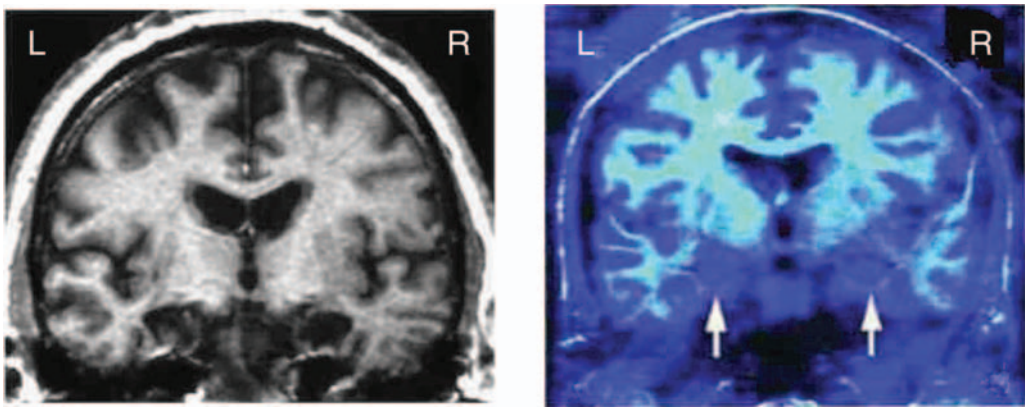


FIGURE 2.3 HM's hippocampal damage. Left: a coronal (i.e. crown-shaped) view of HM's brain, a vertical section from ear to ear. Notice how it compares to the normal brain section on the right. The two arrows on the right side show where the hippocampi are located. In HM's brain we can only see black areas where surgeons removed the extended hippocampal regions. Those cavities have filled with fluid, and appear dark on the brain scan. The two hippocampi are difficult to visualize in these cross-sections, since they are looped and hidden inside of each temporal lobe. (See Figure 2.4.) *Source*: Hodges and Graham, 2001.

The idea of basic differences between autobiographical (episodic), procedural, and semantic memory emerged over many years of study, including human patients, animal lesions, and people with healthy brains. In addition to these memory types, our brains have large *perceptual memory capacities*, long-lasting changes in our ability to perceive the world. For example, learning to hear musical instruments in a new song may involve new perceptual memory capacities. As children grow, their ability to perceive the sounds of speech, the constancy of visual objects, to see faces and identify voices, all become part of their permanent perceptual memories. In the case of Clive Wearing, it seems that his trained capacity to perceive and enjoy music is not impaired. (Experienced musicians can perceive more aspects of a musical piece than novices; i.e. their perceptual memories for music are highly developed.)

There are other long-term capacities. Humans have a vast amount of knowledge about their native language, their culture and the surrounding world. Educated speakers of English can understand some 100,000 words, and each word involves a network of associated knowledge. We have expert skills in processing grammar, discourse, and the interpersonal world. Most of this knowledge is unconscious at any given time (Bargh *et al*., 2006). As far as we know, Clive Wearing's linguistic and semantic knowledge is unchanged, even with his severe brain damage.

Humans live in a rich visual world that we know a lot about. For example, we know that an egg can fall from a table and break, but a table does not usually fall from an egg and break. The oddity of the second idea reflects our vast amount of unconscious knowledge about the visual world. We have no reason to believe that Clive Wearing's and HM's visual knowledge is impaired.

Finally, *declarative knowledge* is commonly defined as our ability to recall facts and beliefs. It is the things we learn in school, which can be 'declared' as propositions. 'China is a large country', 'Whales are marine mammals', and so on. Again, there is no indication that hippocampal damage impairs previously established declarative knowledge. It seems that *existing* knowledge and memory is largely spared with hippocampal patients like HM and Clive Wearing. And yet, according to Deborah Wearing, her husband's life was devastated. His greatest loss was in his capacity to store and retrieve his everyday experiences from memory.

While debate continues about the exact role of the hippocampus itself, there is no doubt about the significance of the hippocampal region, located in the medial temporal lobe (MTL) (Figures 2.4 and 2.5). For that reason, it has become common to refer to the 'medial

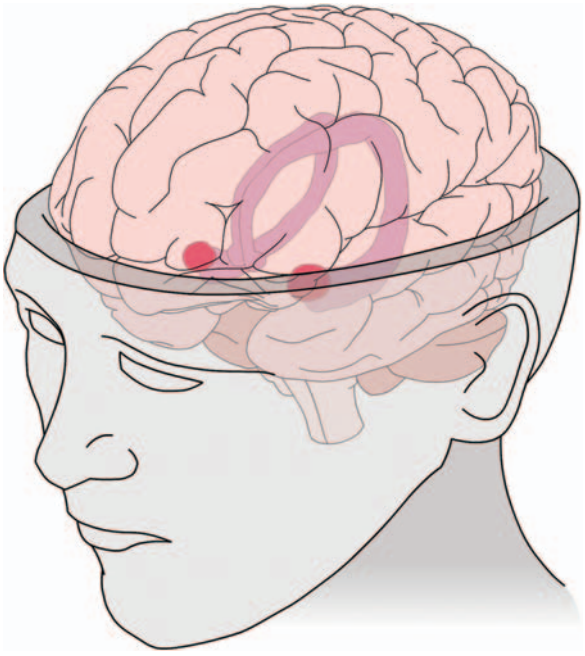


FIGURE 2.4 The two hippocampi. A see-through image of the cortex with the hippocampi nestled inside the temporal lobes. The red bulbs near the tips are the amygdalas, which play a fundamental role in emotion. Surrounding areas of the medial temporal lobe (MTL) also play important roles in memory. (See Figure 2.5.)

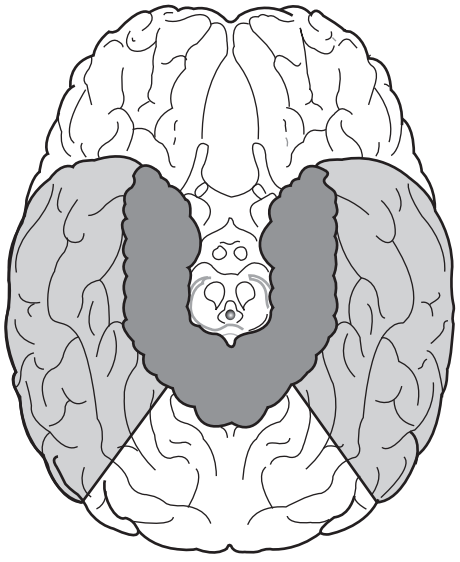


FIGURE 2.5 A bottom view of the brain shows regions removed by surgery in HM. Because more than just the hippocampi are believed to be needed for immediate memory storage, it is now usual to refer to the entire medial temporal lobe (MTL), which is marked. The term 'medial' refers to the midline of the brain, running from front to back.

temporal lobe' or the 'hippocampal complex' as a whole. Notice that the hippocampi are complex spatial structures, a double loop inside each of the temporal lobes but joining across the midline of the brain.

It is easiest to see the medial temporal lobe from the bottom of the brain, which is another important viewpoint of the brain to be able to recognize. The brain is a massively complex organ, evolved over hundreds of millions of years, but packed into a very small space. For that reason, it is often important to recognize a structure like the hippocampal region from two or three points of view (Figure 2.5).

HM is one of the classic patient cases in the history of science, much like Broca's speech-impaired patient in the 1860s. He has been the subject of more than a hundred scientific publications. While HM and others have been enormously important scientifically, the case of Clive Wearing gives us a richer human context. Deborah Wearing has worked for many years to communicate the nature of hippocampal damage to the larger world (Wearing, 2005). Through their personal tragedies, such patients teach us crucial facts about mind and brain.

The two hippocampi – one in each hemisphere – are elongated loops, nestled in the middle of each temporal lobe. The hippocampi and their neighboring structures in the medial temporal lobe cannot be seen from the outside, but they are crucial to our ability to store, work with and retrieve experiences from memory.

2.4 Understanding Clive Wearing in the functional framework

HM and Clive Wearing have lost the ability to move information from their everyday experiences into memory. One hypothesis about this kind of damage is shown in our framework diagram (Figure 2.6). First, consider all the functions that are *not* impaired in hippocampal damage in both hemispheres. Clive Wearing seems to be quite healthy in his sensory functions, including his ability to appreciate music; his conscious experiences and executive control seem normal; so does motor control (though Wearing has some motor difficulties that seem unrelated to hippocampal damage); as we pointed out, some types of long-term memory seem to be unimpaired, except for his

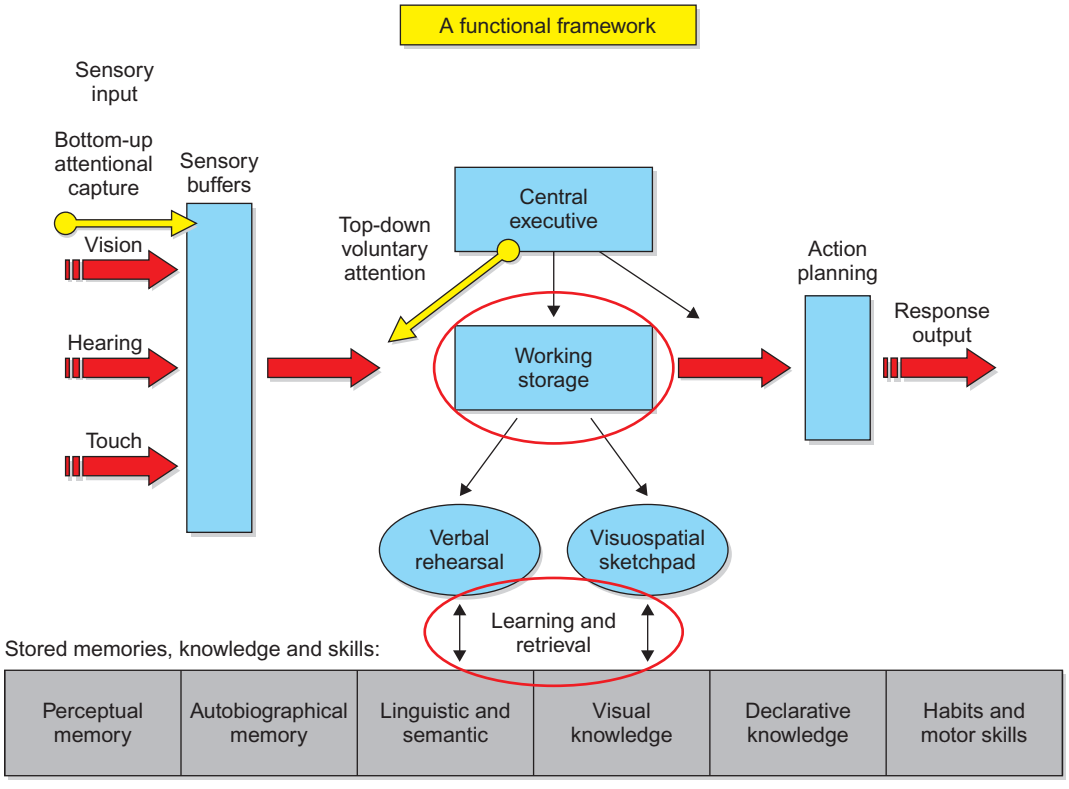


FIGURE 2.6 How medial temporal lobe (MTL) damage can be viewed in the functional framework. Notice that most cognitive functions are spared in classic cases of medial temporal lobe damage in both hemispheres. However, these patients have lost the ability to encode and retrieve conscious experiences – to transfer the present moment to lasting memories and recall them again.

critical inability to store and retrieve his autobiographical experiences; and even his immediate memory persists for perhaps ten seconds. Wearing speaks and understands language at a high level of proficiency. In most tests of intelligence Wearing may score well, except where learning and autobiographical recall are concerned.

Clive Wearing is intensely upset about his condition, showing that he has an understanding that there is something profoundly wrong. His personal relationships with other people are also intensely emotional. It is Clive Wearing's very normality that makes his condition both remarkable and extremely frustrating.

Clive Wearing's crucial loss, therefore, is not in most of the boxes of the functional diagram. It seems that his deficit is primarily limited to the transfer between immediate memory and long-term memory, in both directions: between encoding conscious experiences and retrieving them (Figure 2.6).

2.5 The importance of immediate memory

Immediate memory is needed even for the simplest activities. If you cannot remember the beginning of this sentence you cannot understand its ending. Because a sentence takes several seconds to read, you must be holding information for that length of time. Similarly, if your brain cannot store information from one visual fixation while scanning the rest of your visual field, you cannot put together the separate elements of the scene in front of your eyes (Figure 2.7). Finally, if you need to eat but you cannot keep your goal in mind long enough do something about it, you may end up going hungry. Research over the last fifty years supports the

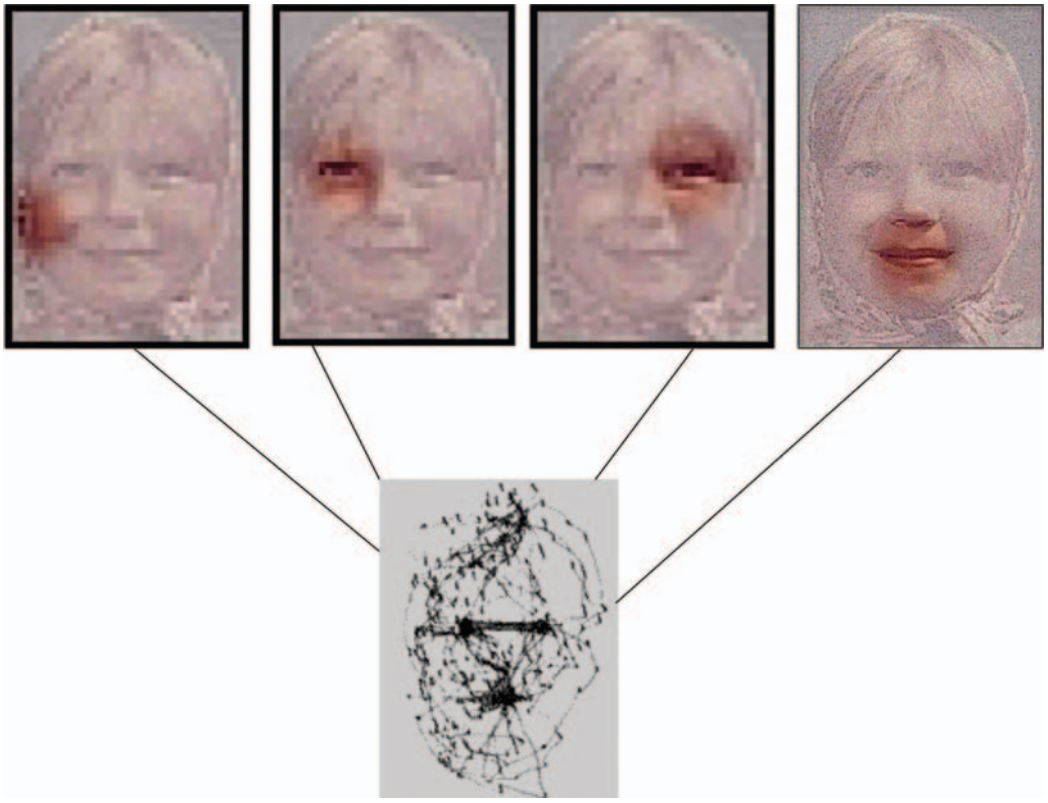


FIGURE 2.7 Immediate memory is needed to integrate small foveal fixations into a single conscious scene. Immediate memory is needed for virtually all cognitive functions. Long eye movements (saccades) jump from one point to another in a visual scene, stopping for only a fraction of a second in the most important parts of the field. At each fixation point the high-resolution part of the retina (the fovea) only picks up a small patch of information, shown by this classic picture from Yarbus (1967; modified by Mark Dubin, used here with permission). The pattern of saccadic movements and momentary fixations are shown by lines superimposed on the girl's face, below. It is believed that the brain stores each foveal snapshot, plans the next saccade, and integrates all the small 'snapshots' into a single coherent visual representation. For that reason an immediate visual buffer memory is needed to integrate many fragmentary records into a coherent conscious scene. *Source*: Adapted from M. Dubin, with permission.

idea that all sensory, motor and cognitive functions require some immediate memory component[1].

Clive Wearing and HM have taught us a great deal. The hippocampal neighborhood continues to be an active topic of research. Because the medial temporal lobe is part of the ancient olfactory brain, which constitutes a large part of the early reptilian and mammalian brain, it has many different functions. The medial temporal lobe is also an area of great convergence between different sense modalities.

Long-term stores may be located in many places, as we will see. These may include the entire cortex, and even subcortical structures like the basal ganglia and cerebellum (see below). But almost everything we can see in Figure 2.1 is the evolutionary more recent cortex, called the *neocortex* (i.e. the new cortex, as opposed to the ancient cortex of reptiles and early mammals). Neocortex expanded greatly over mammalian evolution, accelerating during primate and hominid evolution of the last three million years. The hippocampal regions themselves are called *paleocortex*, or 'old cortex'. While neocortex has six distinct cellular layers, paleocortex has four or five. In humans and other mammals, the hippocampal region is constantly interacting with the neocortex, to encode, maintain and retrieve memories when needed.

The role of the hippocampal complex is one example of the constant interplay between limited-capacity and large-capacity abilities in the brain. 'Limited capacity processes' include conscious cognition, selective attention, immediate memory, and voluntary control. 'Large-capacity functions' include long-term memories, highly practiced skills, and our language vocabulary. We will explore this theme next.

3.0 LIMITED AND LARGE-CAPACITY FUNCTIONS

Even though human brains have tens of billions of neurons, in some ways they have very narrow capacity limits. The limits of short-term memory – the kind we can mentally rehearse – is about 'seven plus or minus two' separate items, as George A. Miller famously described in 1956. That number seems to apply to many kinds of unrelated items – colors, numbers, short words, musical notes, steps on a rating scale, and so on. There are only a few conditions. One is that each item must be consciously noticed for only a brief time; if it is made consciously available many times, it becomes part of long-term memory. Second, the items must be *unpredictable* from previous knowledge. If we simply ask people to remember a rule, like the number series 1, 5, 10, 15, 20, 25 . . . (etc.), they can keep much more information in immediate memory because they only have to remember the rule. When we are prevented from mentally rehearsing items in immediate memory, the capacity of immediate memory drops from about seven to less than four separate items (Cowan, 2001).

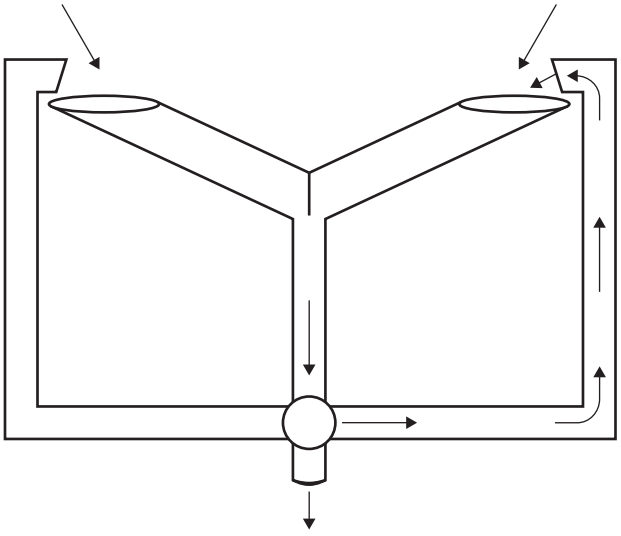
Selective attention is another limited capacity function. It was initially studied by Donald Broadbent and others, using the dichotic listening paradigm (Figure 2.8). In this method, subjects wear headphones with two separate speech channels, often one into each ear. Because they are asked to 'shadow' one of the two channels (i.e. to repeat the incoming speech with minimum lag time), subjects can hear only one channel. It is easy to demonstrate this by listening to two radio news broadcasts at the same time, for example. Under these conditions people can only understand one channel, though they can pick up the voice quality in the unattended channel.

For a gigantic brain, these capacity limits are tiny. Compared to a digital computer, for example, they are astonishingly small. But surprising limits are found beyond immediate memory and selective attention. Table 2.1 shows a dozen other phenomena that show similar, narrow capacity limits.

3.1 Dual task limits

Personal technology has made it possible for us to try to study, listen to our favorite music, and talk on a cellphone at the same time. Sadly, our efficiency in multitasking goes down rapidly the more different things we try to do at the same time. We cannot generally do even two conscious things at a time, such as carrying on a complicated conversation and driving in rush hour traffic. If we don't need to think much about talking, we can drive at the same time, and vice versa, but the more conscious involvement is needed for each task the more they will compete. For that reason, dual-task methods are

[1]There is also evidence for an *intermediate* memory capacity lasting hours or days, but not longer – to remember where we left a bicycle, what food to buy for dinner, how to navigate a new environment, or recent interpersonal events (Delaney *et al*., 2004).



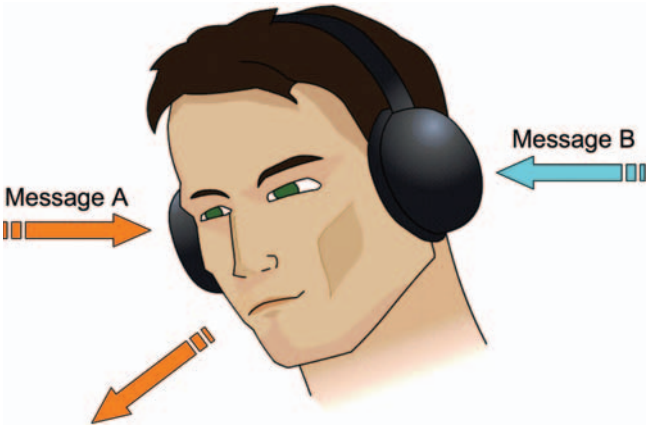


FIGURE 2.8 Donald Broadbent and selective attention. Renewed interest in selective attention emerged in the 1950s with an influential experimental program started by Donald A. Broadbent. The upper image shows Broadbent's 'funnel' image of limited capacity functions, which dramatizes the fact that our large brains have narrow limits for selective attention, conscious perception, and voluntary control. Broadbent's selective listening task, in which two messages are sent simultaneously to the two ears, is a classical dual task method for studying limited capacity functions. *Photograph Source*: From Broadbent, with permission.

often used to study how much of our limited capacity is taken up by a task. As the cognitive demands of one task rise, the efficiency of the second task will go down correspondingly. Dual-task methods have therefore been immensely important in the development of cognitive neuroscience.

How do we cope in the face of capacity limits? There are at least two ways. One is *chunking*, the ability to condense a vast amount of information into a single, organized unit. The words of human languages are often chunks: imagine the amount of information we can access using words like 'mother', 'school', 'love', and so on. We have many other ways of condensing information into single chunks. In studying this chapter, chances are that you will condense it into main points. That is a good chunking strategy, because you can summarize thousands of words into a few dozen sentences.

We can also get around capacity limits by practice. In general, humans are much better with practiced tasks than with novel ones. The brain seems to solve novel problems rather slowly; it makes many errors, and tends to sequence even things that might be done at the same time. Conscious access drops when skills become more practiced and efficient (Raaijmakers and Shiffrin, 1992; Chein and Schneider, 2005). Thus a skilled video gamer may be able to talk at the same time as playing the game, while a novice must concentrate on the game. Practice is a way of lowering the limited capacity cost of doing a task.

TABLE 2.1 Limited capacity tasks

1 Dual-input limits. Some fifty years of research shows that people cannot consciously understand two incompatible streams of information at the same moment.
   a Selective listening: receiving two streams of auditory input at the same time.
   b Inattentional blindness: tracking two competing visual streams on a single screen.
   c Binocular rivalry and its variants: receiving different visual input to the two eyes.
2 Immediate memory limits, including the capacity to hold recalled memories.
3 Ambiguous stimuli and meanings, such as the Necker cube, ambiguous words, and many other cases where input can be interpreted in more than one way.
4 Competition between different features of the same object, such as the Stroop color-naming effect (see Chapter 3).
5 Conjoined feature search: for example, searching for both color and shape in a complex display.
6 Effortful tasks compete against each other. The more difficult two tasks are perceived to be, the more they tend to interfere. There may even be an upper bound on the number of effortful tasks one can accomplish per day (Muraven and Baumeister, 2000).
7 Response competition. Two different output plans or actions tend to compete against each other (Pashler, 1989).
8 Limits on temporal integration:
   a Attentional blink: in a rapid series of visual letters, a 'blind' period may occur some 200–500 milliseconds after a target letter.
   b Change blindness: the difference between two visual scenes may go unnoticed if a brief white flash interrupts them. This may be a limit on the construction of coherent temporal events.
9 Long-term memory search may be limited, as in the case of word retrieval difficulties.
10 Conceptual incompatibility and functional fixedness. It may be difficult or impossible for people to understand an 'obvious' problem from an unexpected point of view.
11 Domain-specific limits. Specific input and output modalities may have local limitations. One example is the very small size of high resolution vision, using the fovea. Another is our difficulty in doing certain bimanual actions, such as patting one's head and rubbing one's stomach at the same time.

TABLE 2.2 Very large-capacity functions

Some brain features show massive capacity.
1 The various kinds of long-term memory.
   a Episodic and autobiographical memory has been estimated to be 1 000 000 000 bits (Landauer, 1986). Using recognition memory, one can retrieve old movie scenes, childhood landmarks, the faces of fellow students, and the like, dating back five decades or longer.
   b Semantic memory for facts and concepts is very large.
   c Procedural memory for highly practiced skills.
2 The language vocabulary: educated speakers of English can recognize about 100 000 words, each of which involves a complex network of related ideas, sounds, and written words.
3 The great complexity of sensory and motor processes.
4 The vast number of neurons, connections, and functional networks in the brain.

However, there is another side to the capacity story. Some cognitive capacities are very large indeed (Table 2.2).

3.2 Some very large brain capacities

At the level of the cells, a structure like the cerebral cortex is immense – a vast, looming starship unto itself, containing, by recent estimates, between 10 and 100 billion neurons. Seen from the outside, it is an elaborately folded structure with many hills and valleys, neatly tucked into the upper half of the cranial cavity. If we could carefully unfold the great cortical mantle we would see a sheet about three feet square ($1\,m^2$), with six layers, each composed of myriads of bushy neurons surrounded by supportive cells. This layered sandwich can be parsed into millions of vertical columns, so that we can imagine a vast six-layered array in three dimensions. Each layer seems to specialize in input, output, or internal connections in the cortex (see Chapters 3 and 5).

Cortical neurons are connected by vast tracts of *axonal fibers*, wrapped in white sheathing cells called *myelin*. If we simply slice through cortex we see mostly white matter, an indication of how many connective fibers there are. To the naked eye, cortex looks like a double fruit covered with a thin skin of cell bodies, the gray matter that we see from the outside. But the white matter contains miles of tiny axons that descend from the gray cell bodies and end up coming back to cortex on

the opposite side of the brain. Current estimates for the left-to-right fibers that cross via the corpus callosum – the large fiber bridge between the hemispheres – is on the order of 200 million. Each of these fibers sends an electrochemical message about ten times per second, making for message traffic of about 2 billion events per second.

An equally large number of axon bundles loop beneath the cortex and come back up on the *same* side. Thus, there is an immense amount of traffic between the two hemispheres, and within each of them as well.

The outermost layer of the six-layered sandwich, Layer I, is so densely woven horizontally that it has been called a *feltwork*, a large skin of tight webbing on top of the sandwich. While most long-distance communication in cortex seems to run through long vertical output fibers (axons), the top layer is so tightly interconnected horizontally that many brain scientists believe there is also a great deal of spreading activity within it.

Cortical neurons do more than connect with other cortical neurons. They also project in vast elegant fiber bundles to the neural organs nestled tightly under the cortex, like small bird eggs in a nest. Among the bird eggs, the *thalamus* serves as a great traffic hub, the way station for almost all sensory messages going to the cortex, and therefore a strategic control point. An equally large mass of fibers goes from cortex to the basal ganglia and cerebellum, both necessary for normal movement.

When we become conscious in the morning, the brain is globally activated, every part showing faster and more widely connected neural traffic. It is as if suddenly all the neurons jumped into their cars and decided to go places. As a novel or surprising event catches our attention, a vast electrical tidal wave rushes all over the brain, a few tenths of a second after the triggering event. This is called the 'event-related potential', discussed in Chapter 4 and in the Appendix.

There is good evidence that anatomical regions in the brain can serve very specialized functions (e.g. Luria, 1976; Geschwind, 1979a). A number of scientists have interpreted the organization of the cerebral cortex in terms of distributed 'unit modules' (Mountcastle, 1978; Edelman and Mountcastle, 1978). Rozin (1976) viewed the evolution of intelligence as an increase in the ability to apply these specialized functions to life situations. Your ability to read, for example, is not something human beings are born with. Unlike heard and spoken speech, babies do not spontaneously learn to read. It takes years of training. But we can learn to use our visual system astonishingly well to take in language by eye rather than ear, and to express language by writing instead of our vocal apparatus. The ability to learn sign language and read in Braille tells the same story. Reading seems to ride on biological preadaptations.

Rozin and others suggest that brain capacities tend to evolve as specialized adaptations. But in the human lifetime, he suggests, specialized functions can become available for new adaptive purposes.

3.3 Why are there such narrow capacity limits?

It would be nice to be able to do half a dozen things at the same time. Why do some functions seem to be so limited in a brain with tens of billion of neurons? It isn't just that we have a limited capacity to *do* things – only one mouth to speak with and two hands to hold things with. Capacity limits also operate in perception, the *input* system, so the limitations of hands and mouth are not the only reason. Ambiguous figures, like the famous Necker Cube, are very limited: we can only perceive one interpretation of an ambiguous stimulus at any given moment.

So the problem isn't just the fact that we can only do one thing at a time in the motor system. And it is not that the brain lacks sheer processing capacity – its ability to store and transform information is beyond our current ability to describe. Some scientists have argued that capacity limits are due to the role of consciousness in combining numerous components of a very large brain into an integrated whole (Baars, 1988, 2002b; Edelman, 1989; Llinas and Pare, 1991). Limited functions are closely associated with conscious experience, while very large capacity functions are generally unconscious (see Tables 2.1 and 2.2). However, it is not clear at this time why that should be so.

3.4 Measuring working memory

The middle column in the figure on page 32 corresponds to classical working memory (Baddeley and Hitch, 1974; Burgess and Hitch, 1999; Baddeley, 2000). Working memory emerged in cognitive psychology several decades ago when scientists began to understand how important immediate memory capacities are. It provides a useful way of thinking about the cognitive brain. More than ten thousand studies have been published on the topic, and working memory is often used to provide a perspective or other functions as well – including mental imagery, language, inner speech, and executive control. The amount of psychological evidence about working memory is immense and, in the last ten years, our understanding of their brain basis has expanded

very rapidly. Working memory therefore offers a convenient and widely understood way of approaching the complexity of the mind and brain.

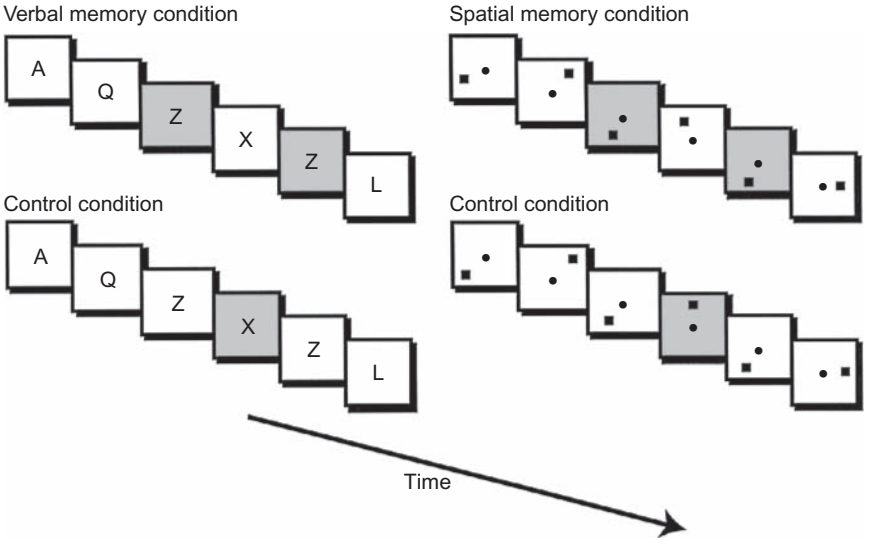
According to Cowan *et al*. (2005), 'Working Memory is the set of mental processes holding limited information in a temporarily accessible state in service of cognition'. This broad definition will prove useful. Working memory has come to stand for the many things we can keep temporarily accessible. Its meaning has broadened considerably since the concept was first proposed in somewhat different words by Atkinson and Shiffrin (1968) and by Baddeley and Hitch (1974). But, in a general sense, the working memory framework has remained quite consistent.

Notice that Cowan's definition is broad enough to allow for expansion to other domains, not just verbal rehearsal and the visuospatial sketchpad. For example, we can imagine mentally humming a song. If we do that successfully, and we can verify it empirically, we could consider adding a working memory component of 'inner music'. Experienced musicians seem to have a number of ways of manipulating notes and melodies in their heads. Athletes can mentally practice sports, and their actual performance improves as a result. Scientists are currently considering different types of working memory for eye movements and emotional processes, perhaps even for dreams and daydreams. Working memory in this very general sense can use a number of different modalities. A great deal of brain and behavioral evidence supports a wider application of these basic ideas.

Once sensory information is attentionally selected, it is often said to become available to working memory. By Cowan's definition (above), that means that an odor or a taste could be 'in a temporarily accessible state in service of cognition'. If you dwell on that definition for ten seconds or so, you are holding your thoughts in working memory. As you can tell, your ability to think about it is vulnerable to distracting events, including your own thoughts and feelings – and reading this sentence. Your ability to think about any topic is therefore capacity-limited. Thus, we might talk about 'thinking working memory', or 'conceptual working memory', as well as visual or verbal working memory.

Measurement is crucial in science, and working memory is typically assessed in several different ways. Figure 2.9 shows one way in which visual working memory may be assessed, simply by presenting visual shapes, in a series of slides over specific time periods, often measured in hundreds of milliseconds. Any stimulus may be presented and re-tested some seconds later, either asking for recall or presenting the original stimulus for recognition. Behaviorally one can assess working memory by accuracy of recall or recognition, and by the speed of responding (*reaction time*).

These simple but powerful methods allow for numerous variations. One popular method is *delayed match to sample* (DMTS), in which subjects are asked to respond



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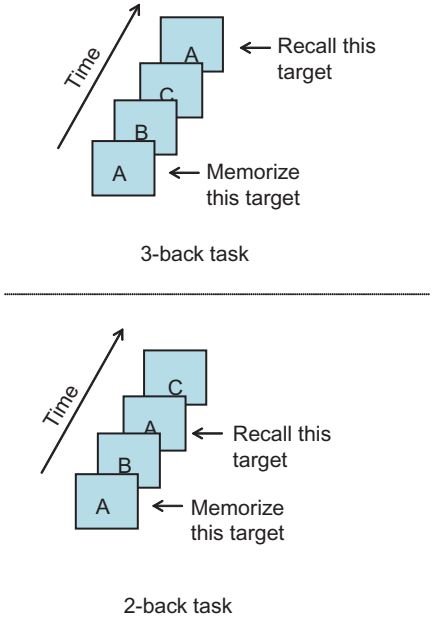

FIGURE 2.10 A difficult continuous memory task: in the *n*-back Working Memory tasks, subjects are asked to recall the item presented one, two, or three slides before. This is a very demanding task. When *n*-back tasks are compared on fMRI, cortical activity increases markedly as *n* goes from 1 to 4. (See Figure 2.11)

when they see a match with their recent memory. This method can be used for animals and infants as well as adults.

What about brain assessment of working memory? Figure 2.10 shows an '*n*-back task', an important variant of the simple WM task. *N*-back tasks allow us to vary the degree of mental workload, a variable that has major brain effects. The concept is fiendish but simple. In any series of stimuli, your job as a subject is to remember the last one you saw – that is fairly easy. But now you are asked to remember the second word you saw *before* the current slide, then the third before, and so on. To do this, subjects must rehearse the last *n* stimuli and not confuse the *n*-back stimulus with the others that have to be kept in working memory.

This is subjectively harder and harder to do as it *n* grows from one to three or four, and the brain shows consistently wider activation. For example, Figure 2.11 shows blood-oxygen changes at the bottom of the brain, using functional magnetic resonance imaging (fMRI) (see Chapter 4). The bottom of the temporal lobe contains many neurons specialized in visual object perception. In addition, it is adjacent to the medial temporal lobe, which contains the two hippocampi. Because this is a demanding executive task – the cognitive equivalent of juggling half a dozen balls at the same time – we also see increased activity in prefrontal regions.

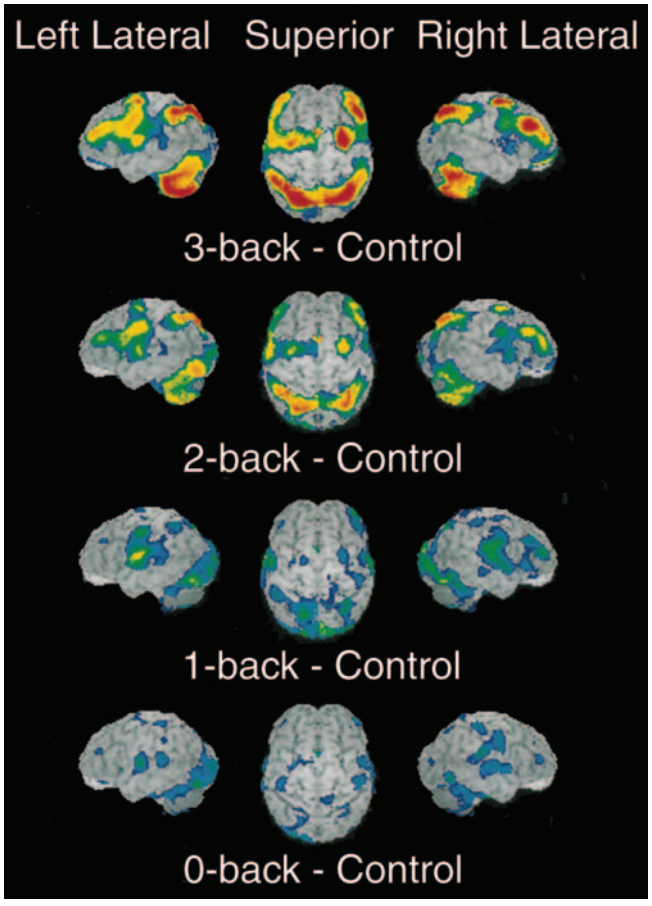

FIGURE 2.11 Brain activity increases with the Working Memory load. Brain imaging using fMRI shows dramatic increases in the amount of cortex involved in the *n*-back task, as *n* rises from 0 to 3. In the 0-back condition, subjects only need to name the visible slide. On these brain images, brighter colors signal higher levels of activity. *Source*: Smith and Jonides, 1997, Figure 10.

4.0 THE INNER AND OUTER SENSES

There is now good evidence that *endogenous* (internally generated) events imitate the outer senses to some degree (Figure 2.12). To see the similarity between them you should recall that the posterior half of the cortex is mainly sensory. Even though our eyes, ears, nose and mouth point forward – the direction we usually move – all sensory pathways terminate in the back of the cortex, where sensory stimuli are analyzed at the highest level.

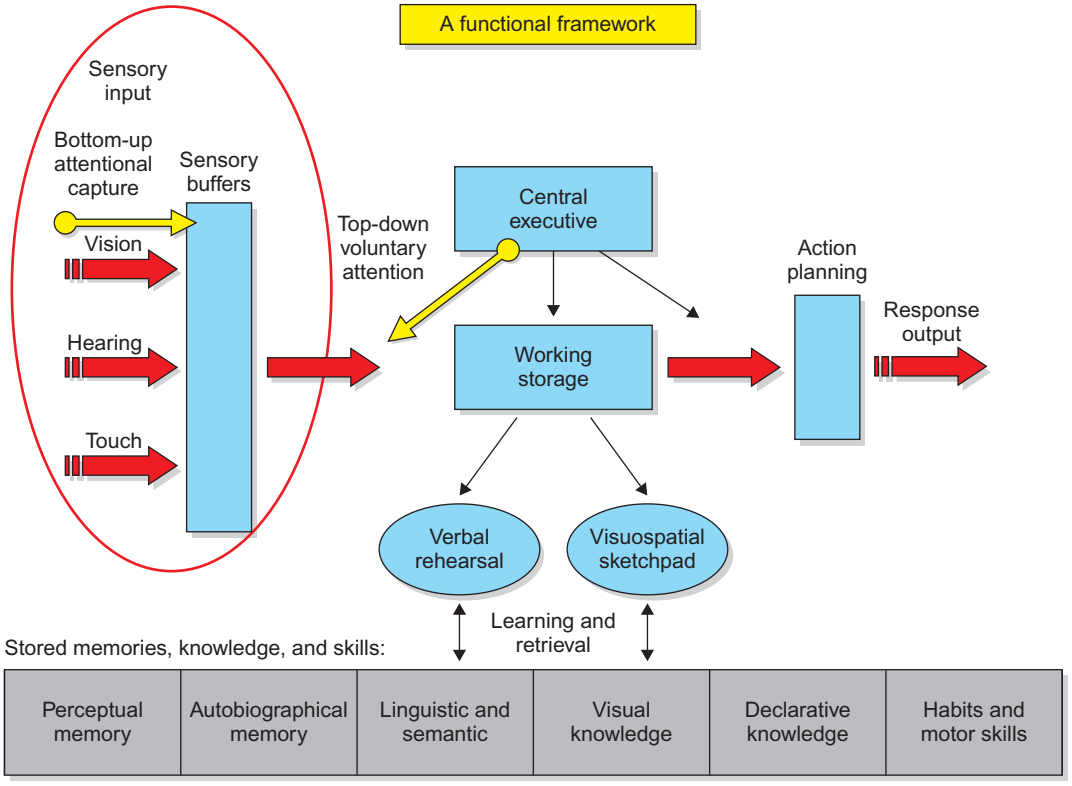

FIGURE 2.12 Framework diagram with sensory emphasis. The sensory systems receive input from arrays of receptors which transform physical energy patterns into neuronal firing. Sensory cortex in vision and the body senses is mapped to the stimulus array in a topographical fashion.

Each sensory pathway reaches cortex in its own *primary projection area*. It is easiest to remember the primary cortices as V1 (for the primary visual projection area), A1 (for primary auditory), and S1 (for primary somatosensory cortex, the body map). V1 is an accurate map of the retinal input (Figure 2.13). It projects in its turn to V2, V3, and so on, each higher visual area representing the visual array in more and more abstract ways (see Chapter 6). As the visual signal traffic flows into parietal cortex, it becomes integrated with hearing, touch, body space, and motor control.

4.1 The mind's eye, ear, and voice

In the 4th century BCE, Aristotle suggested that visual images were 'faint copies' of visual sensations, i.e. he thought that imagery was a kind of vague internal perception. In the last few decades, a mounting body of evidence seems to show he was right. The American psychologist, C.W. Perky, demonstrated this elegantly early in the 20th century when she showed that people can confuse faint visual pictures with their own mental images (Perky, 1910).

Psychologists have devised a number of methods to test visual imagery. Stephen Kosslyn has demonstrated that 'the mind's eye' is a surprisingly realistic figure of speech. The human visual field has a characteristic size and shape, which is easy to demonstrate. Simply look at an object in the room in which you are reading this, allowing your eyes to fixate on a point without moving your head. Now bring your hands in from the sides of your visual field until you can barely see them; the horizontal limits of the active visual field will be on the order of 120 degrees of visual arc. Do the same for the vertical limits, and it will turn out to be less than half of that. The *working* visual field seems to be a flat oval, perhaps 45 visual degrees in height by 120 degrees wide.

If you now close one eye and fix the open eye on a single target, like a single letter in this sentence, the field will shrink dramatically to only a few degrees of visual arc, corresponding to *foveal* vision. The fovea is a small, central patch of each retina that has very high density of visual receptors, hence the highest

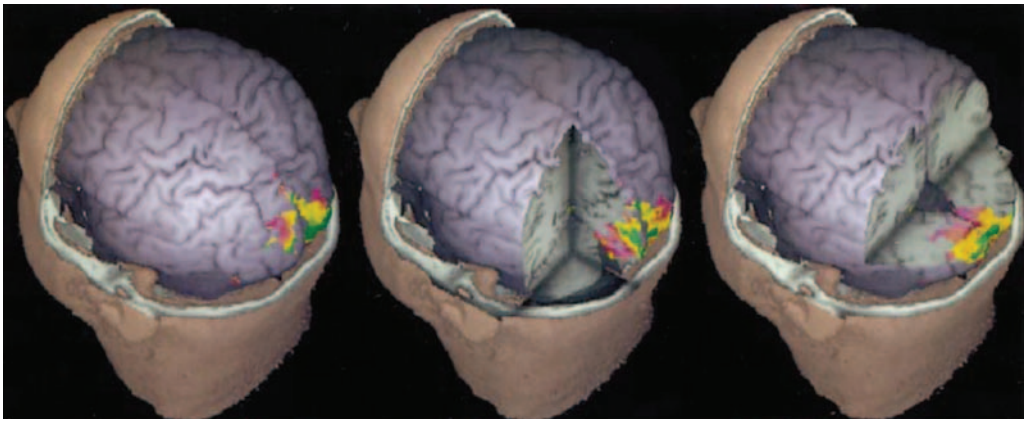

FIGURE 2.13 Occipital activation for visual stimulation. This brain scan shows activation in the occipital cortex, which is mapped point to point to the retinal light input. *Source*: Singh *et al*., 2000.

visual resolution. It is the keyhole-size 'sight' that we aim at the world to get high-resolution snapshots. The fovea subtends about four degrees of visual arc.

You can measure your inner field of your 'mind's eye' in much the way you did with your visual field – naturally, by using your imaginary hands. Closing your eyes, move your virtual hands to the sides of your 'mind's eye', and write down the horizontal extent of your field. Now do the same in the vertical dimension. People generally will come up with somewhat less than 120 degrees of horizontal arc, and about 45 degrees vertical. A variety of such experiments shows a remarkable resemblance between the physical visual field and its mental double. Over the last several years, research has begun to reveal the reason for this resemblance. Kosslyn, Martha Farah and others have shown that visual imagery elicits activity in parts of the visual cortex. Ganis *et al*. (2004) write that, 'Visual imagery and visual perception draw on most of the same neural machinery'.

However, there are many ways of seeing the world, and many ways to use one's visuospatial imagery. Depending upon experimental conditions, different patterns of activity may be found in visual cortex. By using conditions designed to match visual perception and visual imagery as much as possible, Ganis *et al*. showed that brain activity from visual imagery can be nearly identical to visual perception. Figure 2.14 shows that the two activity patterns can be subtracted from each other, point by point, leaving few visible differences. This is a striking result.

Kosslyn (1994) points out that imagery, 'is not a unitary ability, but consists instead of a host of specialized abilities'. The famous mental rotation task devised by Shephard and Cooper (1982), for example, seems to require visual, spatial, motor, *and* executive regions (Figure 2.15). Because V1 has point-to-point mapping to the retina, Kosslyn wrote, 'It is possible that (V1) is activated only by tasks that require high resolution images'.

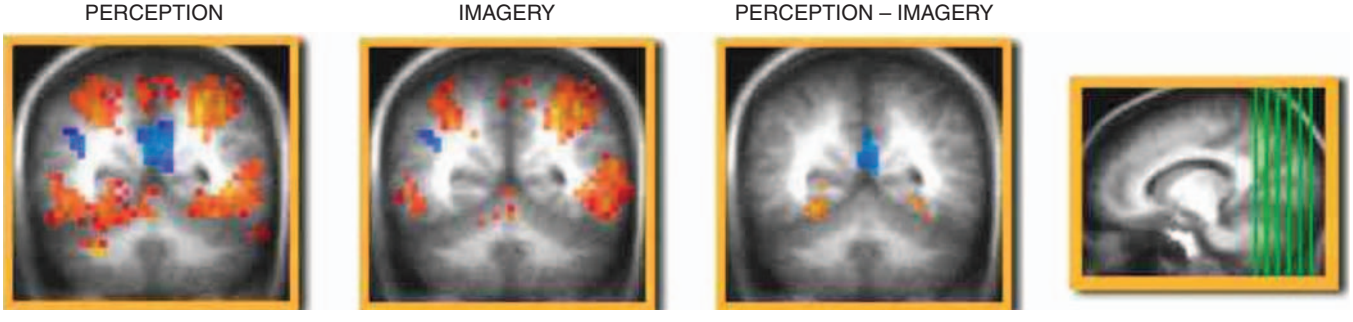

FIGURE 2.14 Visual imagery may activate parts of visual cortex. In these brain scans from Ganis *et al*. (2004), activity for perception and imagery are so similar that they can be subtracted from each other, yielding very little difference. As the right-most figure shows, these virtual slices were selected from the occipital and parietal region. Note that Perception – Imagery means perception *minus* imagery effects. The three images on the left are coronal cross sections cut vertically through the brain with the cerebellum visible at the bottom. On the far right we see a medial left-facing brain. *Source*: Ganis *et al*., 2004. See mini-atlas at the front of this book.

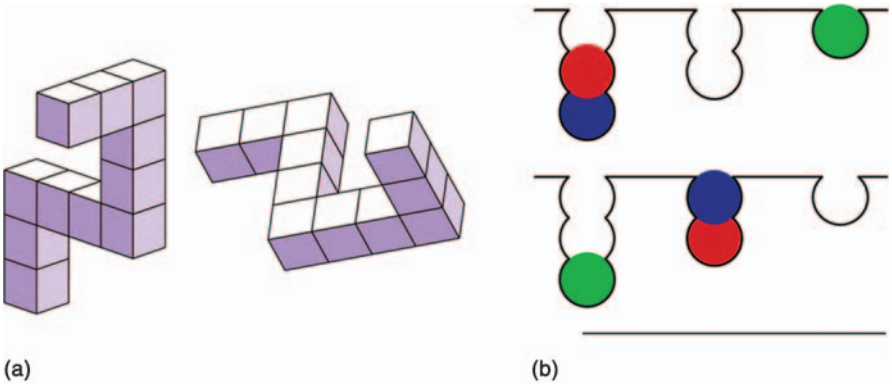

FIGURE 2.15 Different imagery tasks. (a) The classic mental rotation stimuli from Shephard and Cooper (1982). The subject is asked to report whether the two arbitrary shapes are the same or different. To answer the question, subjects mentally rotate one shape to see if it matches the other. (b) A classic 'tower' task, which can be thought of as rolling colored balls from one pocket to another. How can you transform the upper picture into the lower? Here again, subjects appear to use visual imagery, but the task is quite different from mental rotation, or from the task shown. *Source*: Heslow, 2002.

4.2 The imagery sketchpad may use visual regions of cortex

Can you remember the first time you saw this book? If you can, do any visual images come to mind? Can you bring to mind the place and the way the book looked to you? Did you see it lying flat, or propped up? Was it right side up or upside down? People vary in the vividness of their spontaneous mental imagery, but most people can do these tasks. Where does this happen in the brain? Figure 2.14 suggests similar brain regions are active when seeing versus imagining.

Notice how well cognitive and brain findings converge in these examples. Vision involves occipital, temporal, and parietal cortex, and so does 'mental vision' or visual imagery, under carefully controlled conditions.

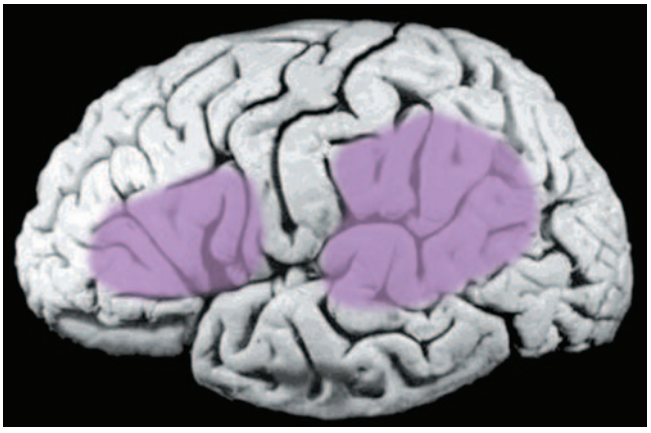

FIGURE 2.16 Approximate location of Broca's and Wernicke's areas. Although 19th century physicians were not equipped with sophisticated brain recording instruments, their conclusions converge well with modern imaging studies. *Source*: Squire *et al.*, 2003.

4.3 Is inner speech like outer speech?

Most human beings go around the world talking to themselves. People are often quite willing to tell us about their private monologue. Simply by asking them to write down clear internal speech as soon as it occurs, a body of useful evidence has been gathered. If we include *inner speech* in the inner senses, we can find similarities between inner and outer articulation of words.

The psycholinguist Gary Dell has shown that internal tongue-twisters create errors very similar to overt tongue-twisters (Dell and Sullivan, 2004). For example, try repeating, 'Peter piper picked a peck of pickled peppers' in your inner speech, as quickly as you can. Do you notice any inner pronunciation errors? But you have no inner tongue to twist – or do you? Imaginary practice can be effective – which makes a lot of sense if we use the same brain tissue for mental and physical practice.

Given what we know about Broca's and Wernicke's areas from Chapter 1 (see also Figure 2.16), where would you predict activation for silent verbal rehearsal?

Mentally rehearsing numbers to ourselves may sound like a vague kind of speech. Scientists have speculated for many years that we actually speak to ourselves silently, and there has been indirect evidence for that hypothesis. It has now been supported by functional brain imaging (see Figure 2.17).

In later chapters, we will see things become a little more complicated, because there are many ways of speaking and listening, and many ways of seeing and visualizing. Yet this is the big picture: it does seem that the 'outer senses' have corresponding 'inner senses', like visual imagery and internal speech (see Figure 2.18).

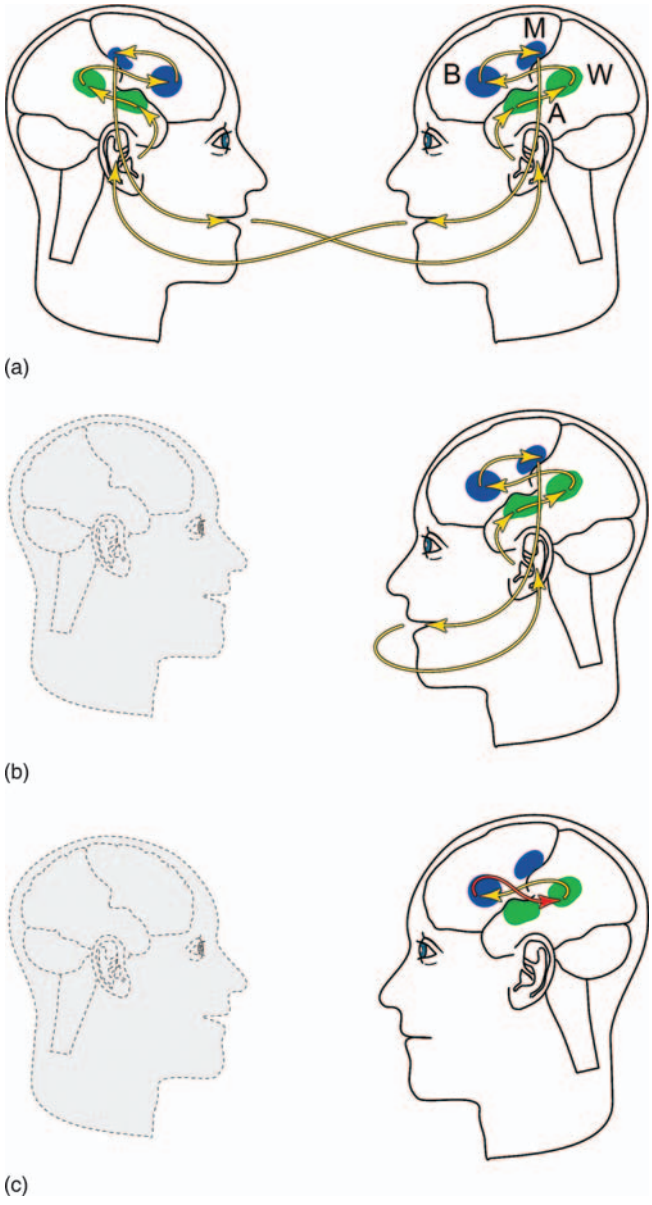

FIGURE 2.17 Inner speech can be considered normal speech (a) with the vocal organs inhibited ('covert'). Covert speech uses the classical speech areas of the left hemisphere ((b) and (c)). A summary brain figure showing some areas activated in an inner speech task. (B = Broca's area; W = Wernicke's area; M = motor cortex; A = auditory cortex). *Source*: Heslow, 2002.

4.4 Is there only one working memory?

We have used the term 'working memory' as if it were a single thing, but that is a hotly debated question. As we will see, there is evidence for both 'domain specific' and 'non-specific' temporary holding memories (see Chapter 8). Some researchers talk about working memories for concepts, for space, and for semantics,

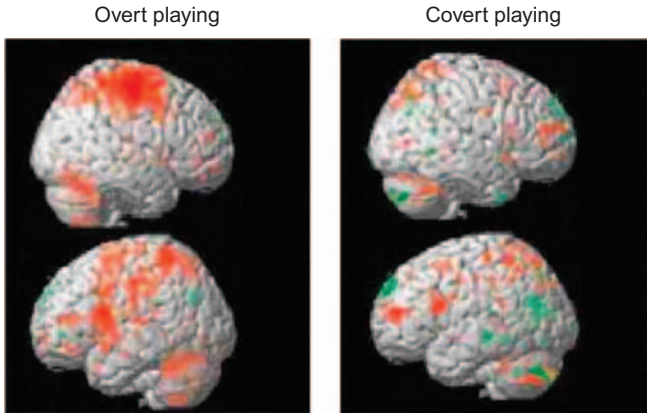

FIGURE 2.18 An inner musician? The 'inner senses' are not limited to verbal and visuospatial abilities. We may have 'inner musicians' and 'inner athletes' as well. These brain scans compare overt and covert instrumental playing by amateur musicians. While overt play shows higher activation in motor and somatosensory areas, generally similar regions of the brain show activity in both conditions. *Source*: Lotze *et al.*, 2000.

as well as vision and speech. Current evidence favors a combination of the two hypotheses: there seem to be both domain-specific and non-specific working memory capacities.

5.0 THE CENTRAL EXECUTIVE

As mentioned before, the prefrontal lobes play an important executive role in the brain. They are needed for voluntary control over actions. Prefrontal regions also support emotional processes and seem to be necessary to control one's own unwanted impulses.

The neurologist Oliver Sacks writes (in Goldberg, 2001b):

> The frontal lobes are the latest achievements of the nervous system; it is only in human beings (and great apes, to some extent) that they reach so great a development. . . . they lack the simple and easily identifiable functions of the more primitive parts of the cerebral cortex, the sensory and motor areas. . . but they are overwhelmingly important. They are crucial for all higher-order purposeful behavior – identifying the objective, projecting the goal, forging plans to reach it, organizing the means by which such plans can be carried out, monitoring and judging the consequences to see that all is accomplished as intended. . . . Without the great development of the frontal lobes in the human brain (coupled with the development

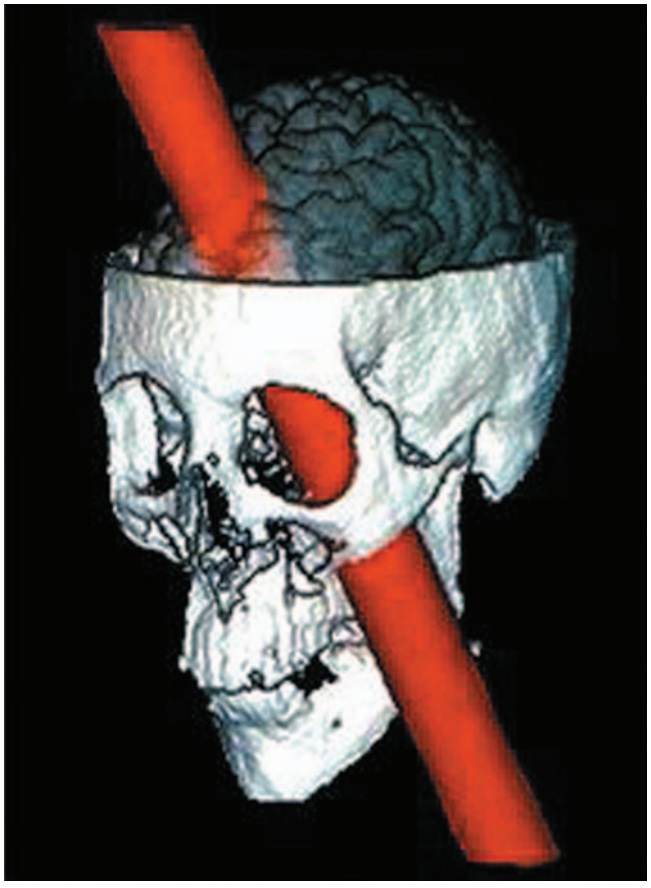

FIGURE 2.19 Hannah Damasio's computerized reconstruction of the brain damage suffered by Phineas Gage in 1848, based on his death mask (Damasio *et al.*, 1994). At the time, most people would have died from an infection of the wound, if not from brain damage and blood loss. Gage was fortunate to survive and recover most of his abilities, but he could no longer pursue his old life goals or control impulsive actions. These changes were so profound as to signal a change in personality. Similar phenomena are observed in other cases of frontal lobe injury (see Chapter 12). *Source*: Caplan and Gould in Squire *et al.*, 2003.

FIGURE 2.20 The Stroop Color-naming Task reflects executive functions. Try to name the colors on top, and you are likely to find it difficult. When the words are unreadable, color naming is easier, faster, and more accurate (bottom half). *Source*: Miller and Wallis in Squire *et al.*, 2003.

of the language areas) civilization could never have arisen.

Thus in the famous case of Phineas Gage (Figure 2.19) – a railway foreman who, while setting an explosive charge in 1848, had a two-foot tamping iron blown through his frontal lobes when the charge backfired – while there was preservation of Gage's intelligence as well as his ability to move and talk and see, there were other, profound changes in him. He became reckless and improvident, impulsive, profane; he could no longer plan or think of the future; and for those who had known him before, 'he was no longer Gage'. He had lost himself, the most central part of his being, and (as is the case with all patients with severe damage to the frontal lobes), he did not know it.

The Stroop Color-naming Task is commonly used to test for frontal lobe damage. In the Stroop Task a conflict is set up between reading a word and naming its color. By using printed color names we can present the word 'blue' in a green color, and ask people to name only the colors as quickly as possible (Figure 2.20). Since educated people are highly practiced readers, their automatic tendency is to *read* the word rather than name its color. The task instructions therefore ask them to do the opposite of what they have practiced doing for many years. In people with healthy brains, the Stroop task sets up a conflict involving prefrontal cortex, but it can usually be resolved. Response times are slowed compared to a control condition, and people sometimes make errors. But, in frontal lobe patients, the effects of the conflict is more debilitating,

leading to more errors, longer response times, and a greater sense of subjective difficulty and frustration. The Stroop Test is useful to probe for subtle frontal lobe damage that may be missed by brain scans.

5.1 Executive effort and automaticity

A remarkable finding from brain scanning experiments is that many different tasks involving executive effort all 'light up' two crucial regions of the frontal brain. On the *sides* of the frontal lobes, this involves the *dorsolateral prefrontal cortex* (DL-PFC)[2]. Along the *midline* of each hemisphere, an important executive region is the front of the cingulate cortex, the *anterior cingulate cortex* (ACC). These areas also show high activity in the Stroop Task, which involves a conflict between highly practiced skills like word reading, and a novel task like color naming (Duncan and Owen, 2000; Frackowiak, 2004).

Voluntary actions become automatic with practice (Shiffrin and Schneider, 1977). As they do so, we also tend to lose some executive control over them (e.g. Langer and Imber, 1979). Our loss of control over highly practiced and predictable habits seems to go along with a loss of conscious access to their details (Schneider, 1995). In brain scans, we see a dramatic reduction of cortical activity when a predictable voluntary action is practiced to the point of automaticity. There is evidence that routinized voluntary actions may be taken over in part by subcortical regions of the brain, notably the basal ganglia and cerebellum.

However, we should not make an all-or-none distinction between voluntary and automatic actions. Automatic actions can come under voluntary control again when predictable aspects of the action become unpredictable, as when we break a leg and try to walk in our usual way (Sacks, 1984). Most everyday activities are a mixture between voluntary and automatic control. The most highly practiced components of our habitual actions tend to be automatic, while the most novel and unpredictable ones tend to remain under voluntary control. Thus, we may be able to make voluntary decisions about which way to walk at a new street intersection, but once we decide to turn right we are rarely conscious of each step we take. The same general point applies to speaking, reading, eye movement control, and much more. Automatic and voluntary control work hand in hand.

An interesting point is the existence of dual-control systems in the brain. For example, we can smile voluntarily or spontaneously (Figure 2.21). These similar muscle actions are triggered by different regions, the voluntary one being more cortical, using the frontal lobes.

Likewise, we can take a deep breath 'at will', but we normally breathe in a spontaneous and automatic rhythm. Large eye movements can also be controlled voluntarily as well as automatically. For smiling, breathing, and eye movements, automatic control is much more common than voluntary cortical control. As we will see, selective attention also has dual control, both voluntary (executive) attention and spontaneous attentional selection.

Such dual control is a common strategy of the brain, but it does not apply to vital functions, like the control of heart rate. For obvious reasons, heart rate control is automatic; it would be disastrous to try to stop or start it at will. The same is true for other autonomic functions. Brain injuries can sometimes dissociate voluntary and automatic control centers from each other, as happens in disorders that impair only voluntary smiles, but not spontaneous ones (see Figure 2.21). There are also brain lesions that work the other way: damage to the brain-stem can cause automatic control to be disabled while voluntary control is spared.

There is a debate whether voluntary actions are equivalent to consciously decided ones (Shiffrin, 1995; Schneider, 1995). This is a difficult issue to settle. However, there is little disagreement that voluntary control and conscious cognition are strongly associated with each other.

Recent evidence also suggests that the executive system corresponds to the 'self of everyday life, (Vogeley

[2]Terms like 'dorsolateral prefrontal' sound intimidating, but are actually quite simple. They are much like the compass terminology 'North, South, East, West, North-West, etc'. 'Dorsal' means 'upper' in the human brain, lateral means 'side', while 'medial' is along the midline. 'Inferior, superior and middle' are what you might expect. We therefore get compound names, such as dorsolateral, meaning the upper part of the side of the cortex, and 'ventromedial', the lower half of the midline of the brain. If that is hard to visualize, it is an excellent idea to draw these directional terms on some visual object, like a picture of a shoe or car. Some students prefer to think of a pair of shoes, to represent the left and right halves of cortex. These objects are useful because they have a clearly defined front, back, left and right side. If you then simply translate the Latin-based vocabulary into words like 'front, back, upper, lower, middle, and sides' you will find it easy to cope with this terminology. We will use a hyphen to separate the directional part from the brain part. Prefrontal cortex is abbreviated as PFC. The upper side part of the PFC is therefore 'DL-PFC'. When in doubt, be sure to decompose the long words into their subunits.

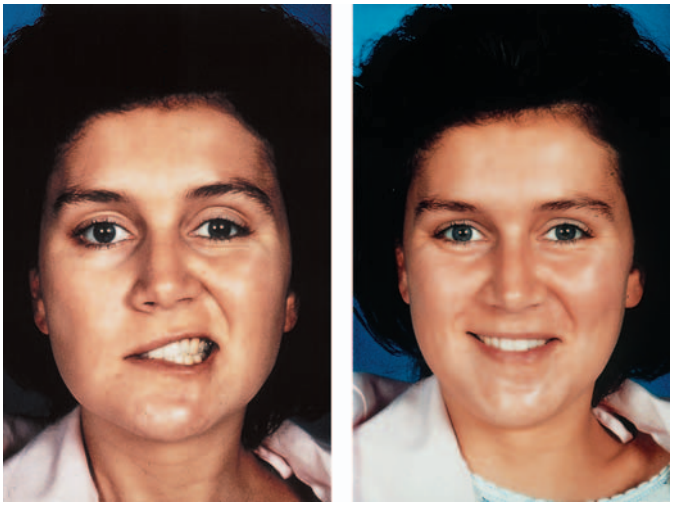

FIGURE 2.21 Selective damage to voluntary but not spontaneous smiles. On the left, this patient cannot make a symmetrical smile, while on the right her smile looks quite normal. On the left, she is trying to smile voluntarily, while in the right photo she is smiling spontaneously. The damage to her frontal lobe motor regions does not affect her (subcortical) facial expressions. Other patients show the opposite damage, impairing spontaneous smiles but not voluntary ones. The ability to show that two brain functions can be damaged independently of each other is called a double dissociation. *Source*: Paxinos and Mai, 2004.

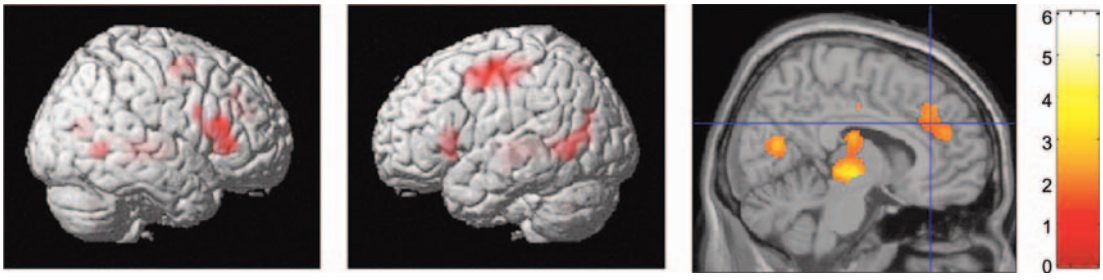

FIGURE 2.22 Posner's model of executive attention. Selective attention is part of the working framework. It can be defined as the ability to select among two or more alternative events. The figure shows the executive attentional network proposed by Posner and coauthors (Fan *et al*., 2005). Notice that two lobes show most activation, the prefrontal and the parietal cortex. Attentional selection can change activity in many regions of the brain. *Source*: Holstege *et al*., 2004.

et al., 1999; Baars, 2002b). We will explore this question in later chapters on executive function and emotion.

5.2 Executive and spontaneous attention

You can decide to pay attention to a single word in this sentence, or the same word could be flashed on and off, so that it tends to compel your attention without executive control. Michael Posner has shown that the executive attention system in the brain involves prefrontal regions, as well as parietal ones, when spatial selection is concerned (Figure 2.22).

The visual 'pop-out' effect is a common example of spontaneous attention (Figure 2.23). Some stimuli come to mind without voluntarily controlled visual search. When the same stimuli are embedded in a field of similar stimuli, the pop-out effect disappears and voluntary search becomes necessary.

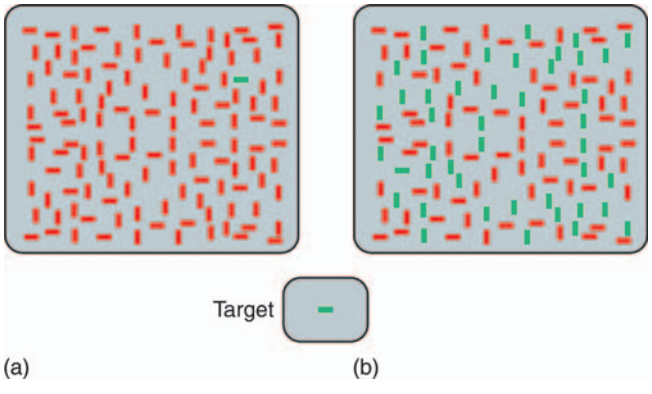

FIGURE 2.23 Spontaneous attentional capture. The task on both sides is to search for the horizontal green bar. On the left side, the green bar appears to 'pop out' spontaneously, with little effort. On the right hand side, finding the green target bar requires effortful search, which is thought to involve executive regions of the brain. Visual 'pop-out' also applies to salient stimuli – ones that are biologically or personally significant, like faces or human bodies, or those that are physically intense. Thus, we have two different kinds of selective attention: voluntary, goal-directed executive attention, and spontaneous, bottom-up attentional 'capture' by salient stimuli. *Source*: Squire *et al*., 2003.

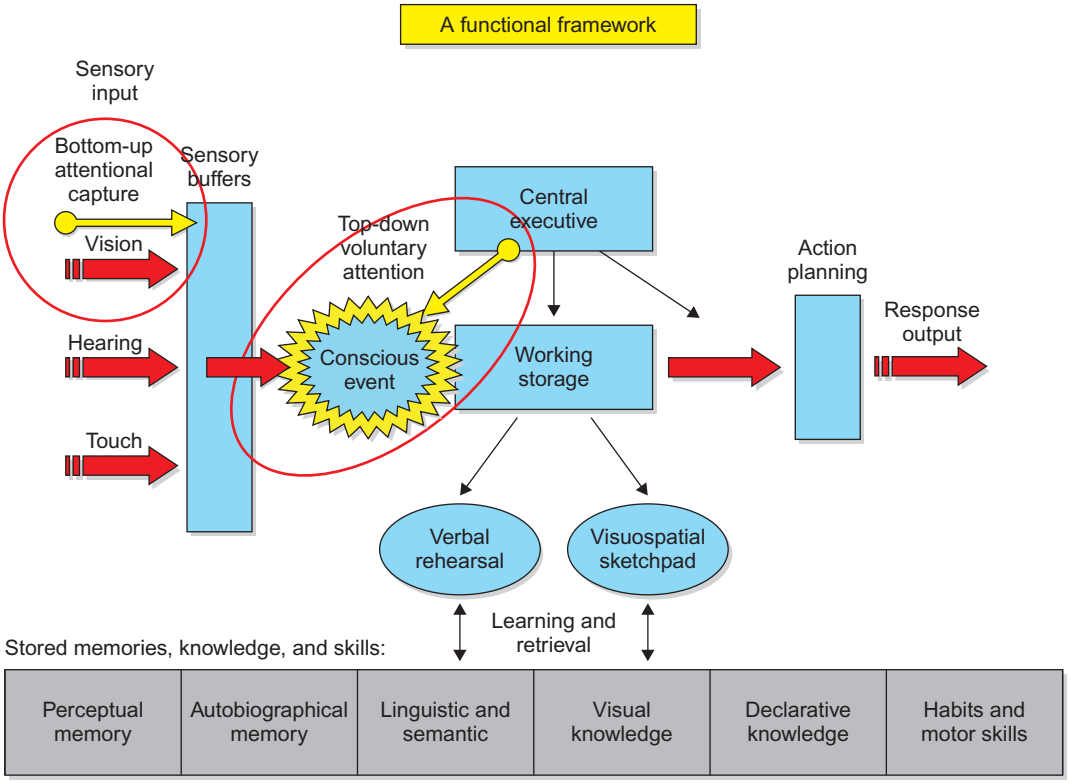

FIGURE 2.24 In practice, conscious events are defined as events that people can report accurately. The functional diagram showing a hypothesized relationship between selective attention and conscious events. A number of scientists believe that selective attention may be needed for conscious sensory experiences. However, there are some contrary findings. A new experimental literature has now grown to explore such questions.

Attention is often thought to be required for conscious experiences. We can represent this hypothesis in the functional diagram (Figure 2.24). As we will see in Chapter 8, this hypothesis is not always true, but in normal life conditions, attentional selection appears to lead to conscious experiences more often than not. The role of consciousness in human cognition has become a hot research topic, and we now have a good deal of evidence that helps to clarify the issue (see Chapter 8). Obviously, there is still a great deal that we do not know about consciousness, but it appears to be a productive topic for scientific research.

6.0 ACTION

The last elements of the functional diagram involve output: control of voluntary actions. There are some striking parallels between perception and action. Fuster (2003) points out that both input and output levels can be viewed as processing hierarchies. The visual hierarchy begins with retinal 'pixels' in cortical area V1, the primary visual cortex, and proceeds to areas specialized for color, motion, and object recognition (see p. 167, Figure 6.11). On the output side, the motor hierarchy begins with general goals, influenced by emotional and motivational input from limbic regions. The most general goals are represented in more prefrontal areas and proceed down the motor hierarchy to supplementary and premotor regions which may trigger intentions and the urge to act (e.g. Penfield and Roberts, 1959). The primary cortical motor region (M1) directly triggers movement of skeletal muscles.

Figure 2.25 shows brain regions that become active in pushing a button with the right hand. The lower right panel shows a time scale marked in seconds, and anticipatory brain activity begins several seconds before the finger press. Notice that motor cortex is active on the *left* side, opposite to the hand that is commanded to move (this is called the *contralateral* side). However, motor cortex activates cerebellar activity on the *same* side as the moving hand (*ipsilateral*) until finally the finger press occurs at the zero point in the time scale.

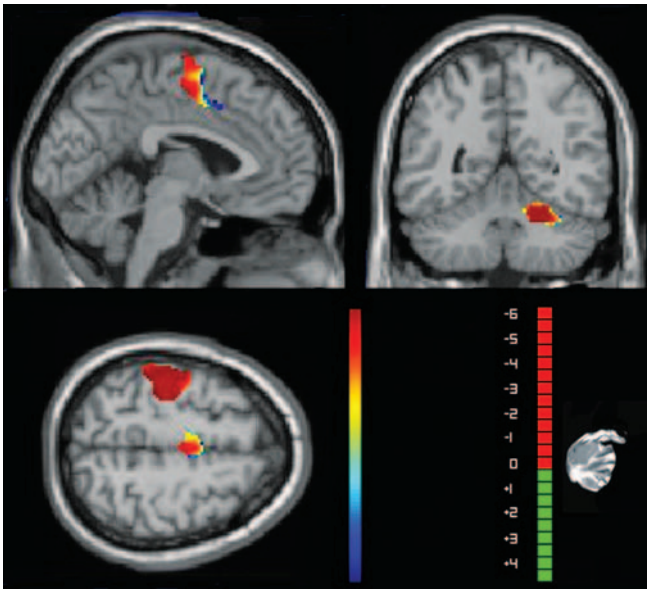

FIGURE 2.25 What the brain does to push a button. Hulsmann *et al*. (2003) has shown how the voluntary goal of pressing a button rises over seconds before a spontaneous action. This snapshot shows the target time (time zero), when the finger press occurs (lower right). The two scans on the left show activation in motor regions of the *left* hemisphere, which controls the right hand. However, the upper right image shows activation on the *right* side of the cerebellum, which is required for fine motor movements like finger presses. This crossover activity is consistent with the known anatomy of motor control. (Note that these brain images do not show other regions known to be involved in action control, including the basal ganglia and motor pathways.) *Source*: Hulsmann *et al*., 2003.

FRONTIERS OF COGNITIVE NEUROSCIENCE

The study of human memory in recent decades

Cognitive neuroscience is an exciting new field encompassing the formerly separate disciplines of biology and psychology, now united in the ongoing quest for understanding the mind and the brain. An influential leader in this quest is Dr. Larry Squire, Distinguished Professor of Psychiatry, Neurosciences, and Psychology, at the University of California, San Diego School of Medicine, who has long studied the neural bases for long-term memory.

We sat down with Dr. Squire and discussed the metamorphoses of the study of human memory over the past several decades. Here are some highlights of that discussion.

Humans have long been fascinated by our memories — how they are formed, how some memories from long ago still seem so vibrant to us today, and how they can be damaged or lost. The modern era of the study of memory began with a seminal paper published in 1957 by Dr. Brenda Milner (Scoville & Milner, 1957).

It all began when she and Dr. Wilder Penfield, the famed neurosurgeon, were studying two patients who had unilateral removal of structures in the medial temporal lobe as part of treatment for intractable epilepsy (Penfield & Milner, 1958). An unexpected result of the surgeries was that the patients experienced severe amnesia: loss of memory. These case studies were presented at a scientific meeting in 1955 and shortly thereafter, Dr. Penfield received a call from Dr. William Scoville, a neurosurgeon from Hartford, Connecticut. It seems that

FIGURE 2.26 Larry R. Squire, PhD, University of California and the Veterans Affairs Medical Center, San Diego, CA, USA.

he had a similar result — severe amnesia — in a patient who had medial temporal lobe structures removed bilaterally. Dr. Milner traveled to Hartford to study this patient, a young man of 29 who had suffered from epilepsy since childhood due to a bicycle accident. In 1953, his epilepsy was so severe that Dr. Scoville decided to surgically remove brain structures in the medial temporal lobe, including the hippocampus. The epilepsy was controlled, but the young man, known as patient HM, was never the same: his memory was forever damaged. HM became a cornerstone in the study of human memory and the role of the hippocampus. His death in December 2008 allowed scientists to finally release his name and more details of his landmark case (Squire, 2009).

Reports of the damage to HM's memory due to the surgery launched a veritable sea of new studies about the role of the medial temporal lobe and, specifically, the hippocampus, that continue to this day. Three fundamental principles emerged from the study of HM: (1) memory is a distinct brain function, separable from general cognitive and language functions, since HM's intellect and ability to produce and understand language were intact; (2) the medial temporal lobe is not necessary for immediate memory, since this was largely normal in HM; and (3) medial temporal lobe structures are not the final storage location for memories, since although removal of these structures induced severe amnesia in HM that spanned many years in the past, he still retained memories of his childhood. Another key finding from the study of HM was that human memory was not a monolithic system: although clearly separable from general cognitive function, memory nevertheless was comprised of subcategories or systems. HM, although severely amnesic, was able to learn new tasks and procedures. Out of the careful study of what was impaired and what was intact in HM, Dr. Larry Squire and other memory researchers began to develop theories for separable aspects of memory.

The next four decades produced a wealth of new knowledge about memory in the brain: early studies focused on lesion approaches, studying human patients who had damage to the medial temporal lobe and experimentally "lesioning" these regions in laboratory animals. The emergence of new techniques in molecular genetics and functional neuroimaging in the 1990s launched a new sea of investigations of the genetic and neural bases for memory.

Dr. Squire has played a central role in these investigations: using a multidisciplinary approach that encompasses lesion studies in human, lesion studies in nonhuman primates and mammals, genetic research, behavioral studies, and functional neuroimaging investigations, Dr. Squire has been a leader in the quest to elucidate the brain bases for memory. Recent findings are shedding new light on the functional role of the hippocampus in memory. Cumulatively, these findings suggest that the hippocampus is initially highly involved with the cortex in the support of long-term memory storage but that this role gradually declines over the years. Thus, there is a graded change in the role of the hippocampus with respect to the final repository in the brain of long-term memories: this notion is well-supported by early observation that HM did recall early childhood memories despite his severe amnesia. Other new findings are related to sleep and the role of the hippocampus in memory consolidation. Recent findings support an idea of a dialogue that takes place between the hippocampus and the cortex during sleep, which may reflect how recent memories become long-term and lasting (Squire, in press).

Where do we stand today? Dr. Squire has developed an overarching theory for long-term memory systems and the brain structures that subserve them that has

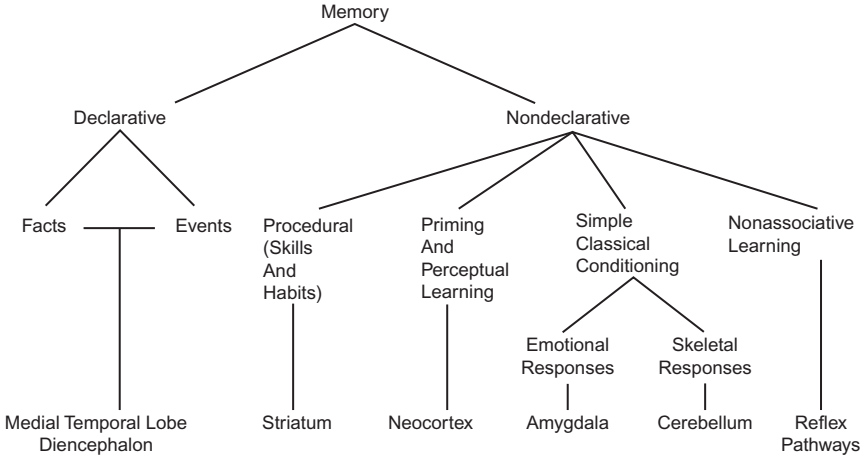

FIGURE 2.27 Schematic/taxonomy of mammalian long-term memory systems. *Source*: Squire, 2004.

been highly influential in the study of human memory (Figure 2.27; Kandel & Squire, 2000; Squire, 2004). Where are we heading tomorrow? No one knows, but it is likely the development of new methods and techniques for investigating brain bases for memory will serve to jump-start our knowledge on the topic of memory.

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7.0 CONSOLIDATION OF SHORT-TERM EVENTS INTO LONG-TERM MEMORY

Clive Wearing was able to experience the present moment, but he could no longer store that experience in long-term autobiographical memory. Long-term stores are shown in the functional diagram along the bottom, ranging from perceptual memory to highly practiced habits (Figure 2.28).

The question of where long-term memories are stored in the brain continues to be one of the mysteries. However, there is a great deal of indirect evidence for the *consolidation hypothesis*, suggesting that memory is stored in the same areas that support active moment-to-moment brain functions. Working memory changes quickly and is vulnerable to interference because it depends on dynamic electrochemical activities in large populations of neurons and synapses. After enough rehearsal, however, the synaptic connections needed to

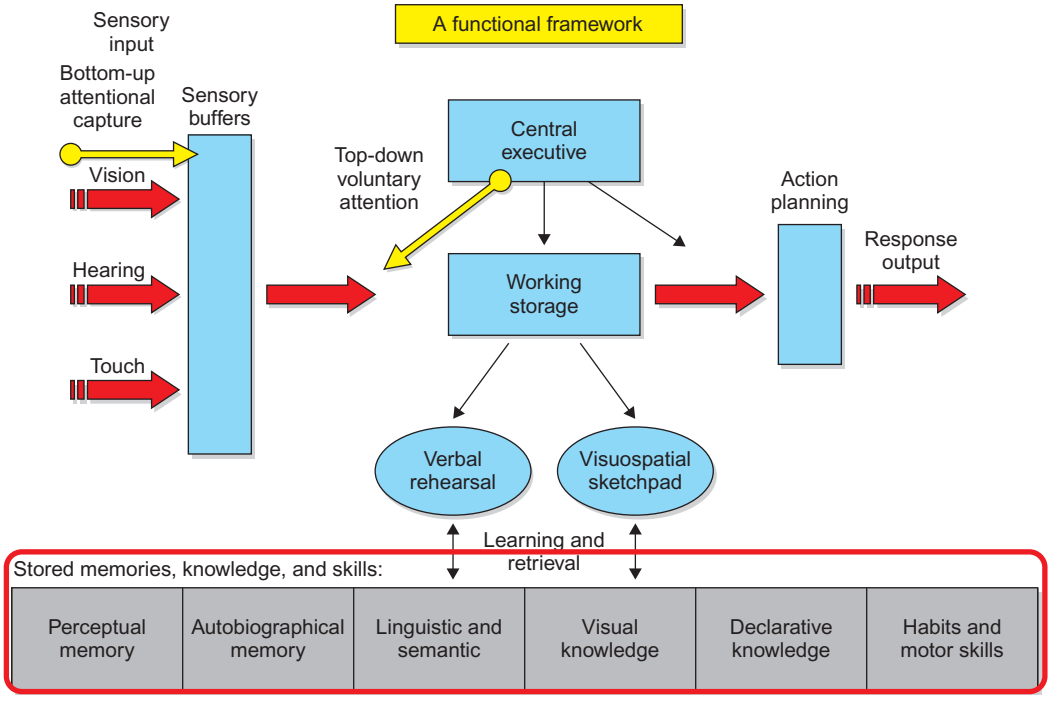


FIGURE 2.28 Long-term stores are shown in the functional diagram along the bottom, ranging from perceptual memory to highly practiced habits. When memory stores are not activated, their contents are unconscious.

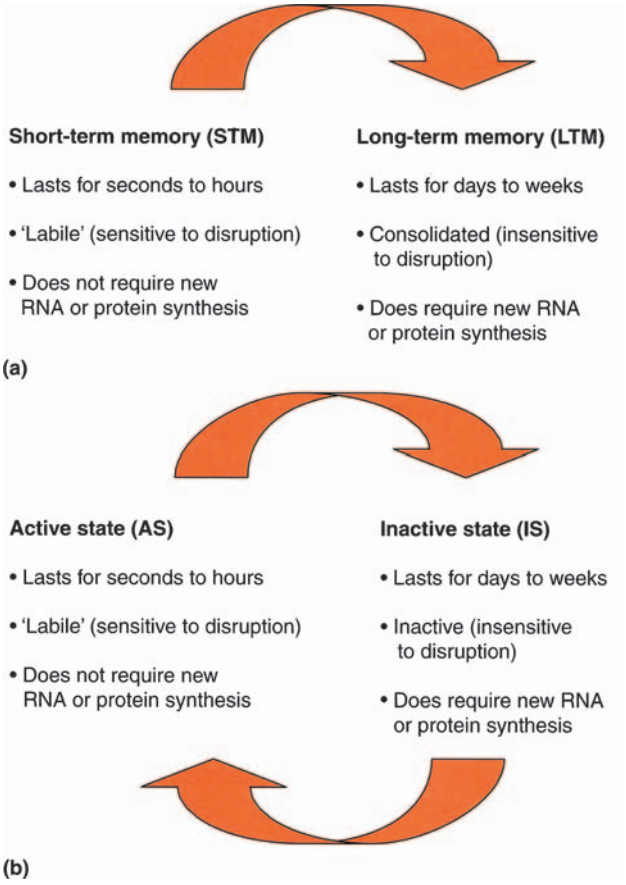


FIGURE 2.29 Transient memories become consolidated over time. Short-term memories are subject to interference, probably because they involve active neuronal circuits in the brain. If information is retained over a period of seconds to hours it may become permanent or 'consolidated'. A good night's sleep is now known to facilitate memory consolidation. Long-term memories are believed to require protein synthesis, which increases the efficiency of synaptic connections. *Source*: Nader, 2003.

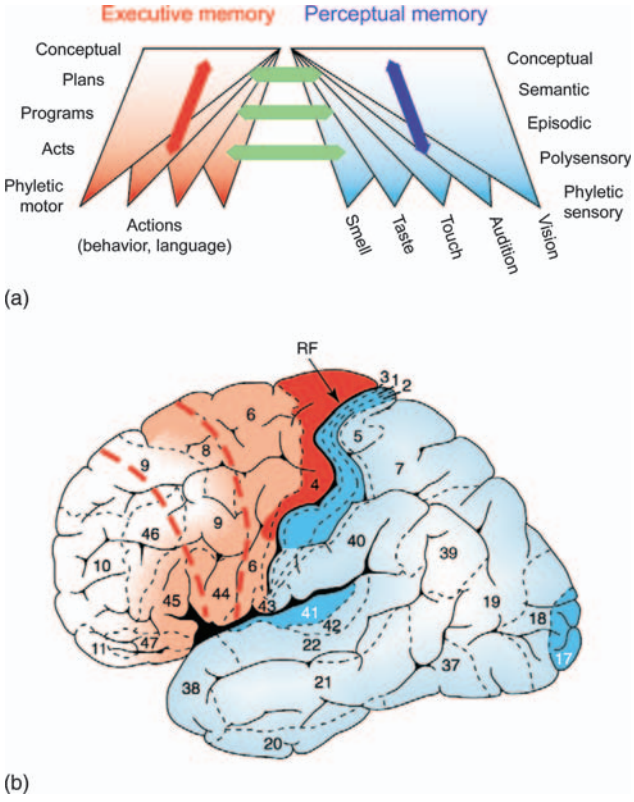


FIGURE 2.30 If the consolidation hypothesis is true, memory may be stored in many different regions of the brain by means of long-lasting synaptic connections. Fuster (2003) suggests, therefore, that the rear (posterior) half of cortex can be thought of as involving sensory memory systems, and the frontal half may involve executive and motor memories. In addition, the hippocampal neighborhood is certainly involved with episodic memory (memory for conscious experiences), while subcortical areas like the basal ganglia and cerebellum play a role in motor learning. Fuster's hypothesis provides a useful way to think about the brain basis of long-term memory. *Source*: Fuster, 2003. (See p. 124 for details.)

store memories are thought to become more efficient and longer lasting. Figure 2.29 suggests that dynamic synaptic contacts are converted to more permanent connections, using protein synthesis and RNA. The traditional slogan for the consolidation hypothesis is: 'Neurons that fire together, wire together' (see Chapter 3).

A number of memory theorists propose that long-term memory traces may be stored in the same areas of the brain that are involved in their active forms. Figure 2.30 by Joaquin Fuster illustrates this point about the cortex. The figure shows the posterior half of cortex (shades light blue) is mostly involved with sensory functions, and is thought also to store sensory and perceptual memories. As mentioned above, the frontal half involves executive functions, motor control, Broca's area, and other cognitive functions, and may therefore be involved in consolidating memory for those functions (see Chapter 5).

The consolidation hypothesis provides a useful simplification of much evidence. Long-term memory is covered in detail in Chapter 9.

7.1 Is working memory just re-activated permanent memory?

The consolidation hypothesis raises an interesting question: is it possible that immediate memory just activates long-term traces encoded in the brain? We can look at this question from both long-term and

TABLE 2.3 Some brain hypotheses for the functional framework

Sensory input and sensory stores	Sensory cortex (posterior half of cortex), as well as sensory pathways and thalamic relay nuclei
Voluntary selective attention	Prefrontal and parietal regions may modulate sensory cortex to select some input signals over others
Spontaneous selective attention	Sensory regions may trigger orienting and selective signal processing
Verbal WM	Extended Broca and Wernicke's areas, prefrontal cortex, and medial temporal lobe
Visuospatial sketchpad	Visual cortex, including the parietal lobe and prefrontal regions
Response output	Prefrontal and motor cortex, basal ganglia, cerebellum and motor pathways
Transient storage of WM	Medial temporal lobe interacting with neocortex
Long-term memory systems	Lasting changes in cortical connectivity

short-term memory perspectives. At this point, you may want to keep this possibility in mind – just to remind yourself that all of today's ideas in cognitive neuroscience may be seen from more than one point of view. It is important to stay open until the evidence is beyond dispute.

Table 2.3 suggests some possible brain regions for the cognitive framework. Later chapters will explore these hypotheses in greater detail.

8.0 SUMMARY

This chapter has explored a broad functional framework for cognitive neuroscience, based on widely accepted ideas. We have also shown some brain correlates of the functional framework.

Chapter 1 summarized some history about Broca's and Wernicke's studies of the speaking hemisphere, and this chapter shows how those regions seem to be involved in internal speech (verbal rehearsal). Similarly, visual imagery seems to make use of visual cortex, and even 'inner music' may involve brain areas involved in overt music listening and playing. As a simplifying hypothesis, we can therefore look for similarities between overt and covert cognitive functions. This tentative hypothesis will aid in understanding later chapters.

Immediate memory seems to depend on the medial temporal lobe, including the two hippocampi and their surrounding regions. Damage to those regions impairs the ability to transfer information from the present moment to long-term storage. The consolidation hypothesis suggests that long-term memory may be a permanent strengthening of the active connections established by current experiences held in working memory.

The rear half of cortex is involved in sensory processes, and probably also in sensory-perceptual memory. The front half of cortex is involved with motor and executive functions, and probably also with long-term memory needed for those processes. Indeed, immediate memory can be looked at the other way, in terms of long-term capacities that are evoked by current input.

Selective attention has been studied for some fifty years and, in the last 15 years, the traditional question of conscious experience has again come to the fore. As we will see, it has been studied using many different experimental methods. Conscious cognition complements the other features of the functional diagram (see Figure 2.24).

It is important to hold these ideas lightly as a way of thinking about cognitive neuroscience. They will be tested in more detail in later chapters.

There is ongoing debate about the meaning of terms like 'working memory', 'attention', and 'conscious experiences'. Such debates are common in science. We have a reasonable working consensus today, however, about empirical definitions – the kind of evidence that is believed to tell us about these concepts. In practice, 'working memory' has come to mean any brief memory phenomenon, on the order of tens of seconds, that allows us to retain and manipulate information. Simply remembering a telephone number while reaching for the phone fits this definition. So does mental arithmetic, and thinking about the best route to take in walking from one place to another. Working memory was first explored by giving people lists of unrelated words or numbers, and asking them to recall them ten to thirty seconds later. Another popular approach is 'delayed match to sample', in which people are given a stimulus to remember and are asked to respond 'yes' or 'no' when they see it.

Delayed match to sample (DMTS) is commonly used in animal studies, since we cannot ask rats or monkeys to report their experiences. Perhaps we can think of successful matching to a past event as a kind of reporting. Animal studies have been an important source of evidence. For example, they helped confirm

the role of the hippocampus in learning. In practice, the defining feature of 'working memory' is the ability to hold an item in memory for several seconds. This reasoning has been applied to working memory for odors and even planned eye movements.

There has been a wealth of new knowledge learned about human cognition and the brain. It is an intricate business to tease apart these aspects of human thought and action experimentally. While the field has made progress in understanding how these areas of cognition interact, we have far to go before we will have a clear understanding of the dynamic integrative and interactive processes that underlie the human condition.

9.0 STUDY QUESTIONS AND DRAWING PRACTICE

9.1 Study questions

1 What have the cases of Clive Wearing and HM taught us about memory?
2 What brain areas are believed to be involved in working memory and long-term memory? In visual imagery and spatial planning?
3 What is inner speech and how does it relate to everyday cognition?
4 Which brain landmarks could you use to tell where the eyes are looking? Where is the back of the head? The left side? The right side?
5 What is a useful definition for working memory? For selective attention? For the different types of long-term stores?

9.2 Drawing exercises

1 Label the Framework in Figure 2.31.
2 Label the colored functional regions in the brain diagram in Figure 2.32.

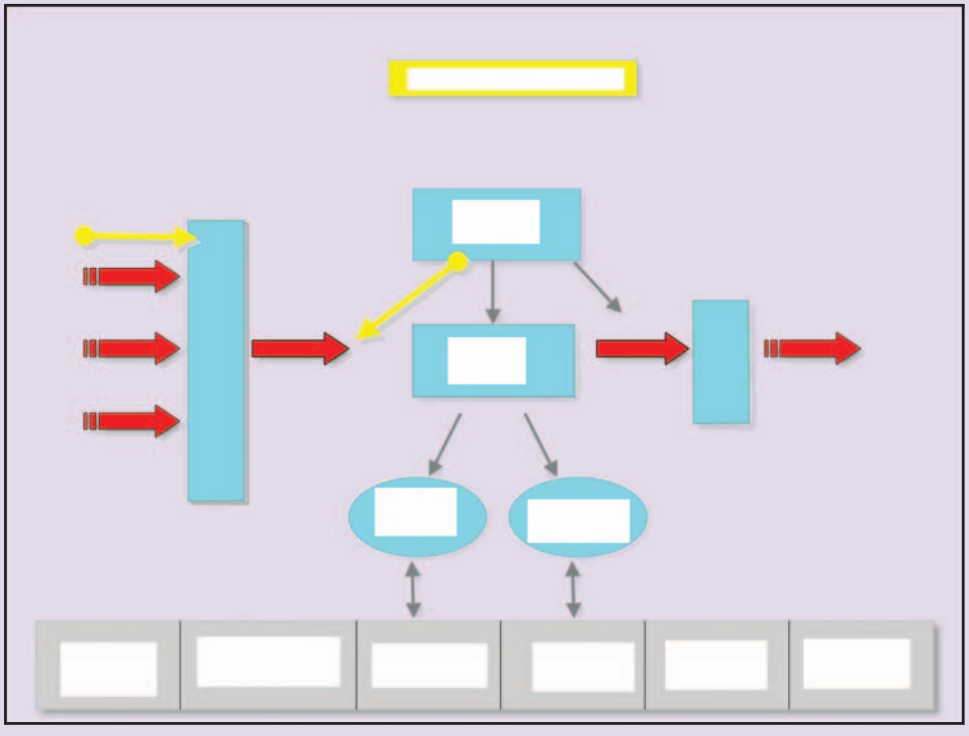


FIGURE 2.31

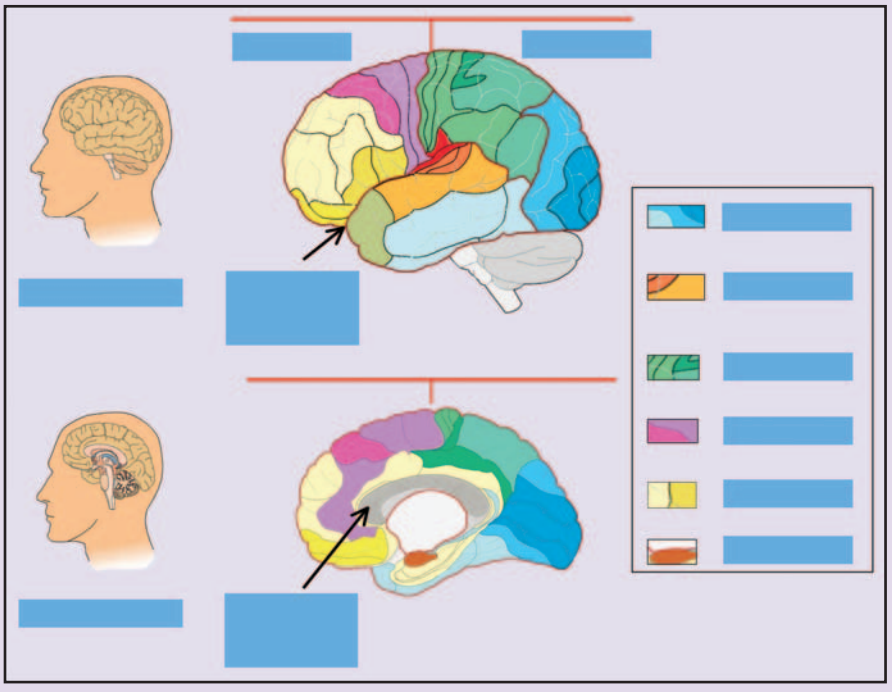
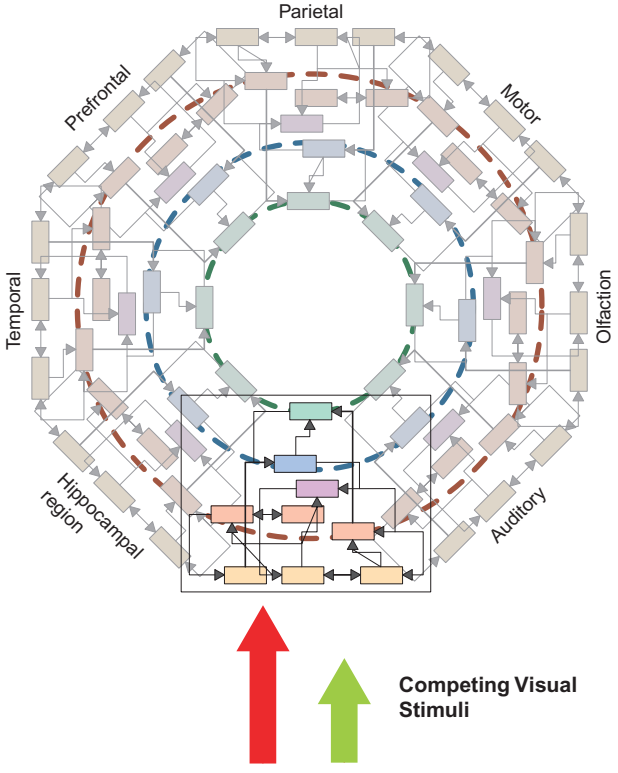


FIGURE 2.32

There is no more important quest in the whole of science probably than the attempt to understand those very particular events in evolution by which brains worked out that special trick that enabled them to add to the scheme of things: color, sound, pain, pleasure, and all the facets of mental experience.

Roger Sperry (1976)



How neurons are often organized. It is helpful to think of neurons in the cortex (and many other structures) as layered hierarchies. In the cortex, signals can flow in any direction. The figure shows a circle of such layered hierarchies, allowing communication between auditory, visual, and other regions. *Source*: Modified from Friston, 2003.

CHAPTER

3

Neurons and their connections

OUTLINE

1.0 INTRODUCTION

Chapter 2 gave a first overview of brain functions like perception, working memory, attention, and executive control. These have become easier to study since the discovery of brain imaging methods. But what do we know at the level of the neuron? Can we tell a plausible story at a more detailed biological level?

We begin with some basic ideas about neurons and their connections. In Chapter 1, we pointed out that science always makes inferences that go *beyond* raw observations, using abstract concepts that 'make a believable story'. Neurons have been studied for two centuries, and the simplifications we will use here are well based in evidence. But, like any other simplified story, this one may encounter surprises. If it does, we must change it accordingly.

Brains are made of signaling cells – neurons – which are highly conserved over evolution. That is, they have remained relatively stable over hundreds of millions of years, as suggested by the fact that very different animal species have similar kinds of neurons. In most respects, neurons are like other body cells, but they are highly specialized for electrochemical signaling: they accept

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

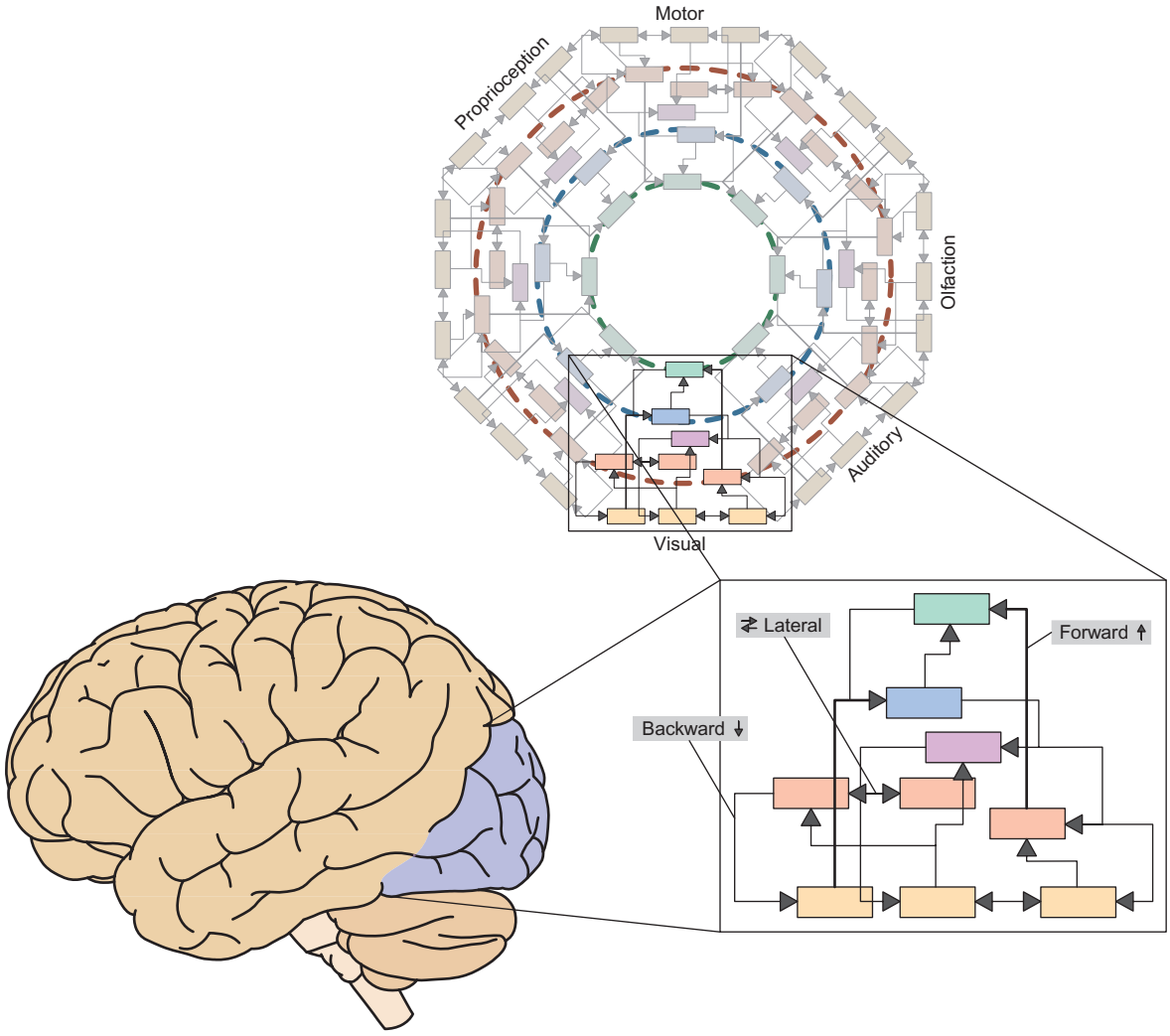


FIGURE 3.1 Neurons, networks, and the brain. Three levels of description, from neurons to large 'nets of nets'. Sensory and motor cortex are often viewed as processing hierarchies (Friston, 2003). In this example, visual maps in the occipital lobe go from simple (V1) to complex representations of the visual world, flowing deeply into the temporal and parietal lobes. The upper circle of hierarchies represents the overall architecture of the cortex. *Source*: Friston, 2003.

input at their dendrites from other cells, and send an electrochemical signal along an output branch, the axon. The entire brain can be viewed as a hypercomplex surface of neurons and their connections (Figure 3.1).

Dendrites and *axons* are thin micron-level tubes extruding from the cell body; an average neuron may have ten thousand input branches, and one or more output fibers (Figures 3.2 and 3.3). Nerve cells fire their spikes much more slowly than the electronic arrays that run computers, but they still do some things far better than current computers. Computers do not reach human performance at this time in terms of perception, language, semantic memory, action control, or artistic creativity.

1.1 Real and idealized neurons

The brain is a kind of Amazon rain forest with many undiscovered species of trees, plants, and animals. To begin we will focus only on one prototypical tree, but this is only a convenient fiction. The great diversity of the neurons in the brain is suggested by Figure 3.4 – there are many classes of neurons, neurochemicals, and potential mechanisms of information processing. Our first simplification, therefore, is to focus only on an *integrate and fire neuron* (see Figure 3.3). This classical neuron accepts input from other nerve cells in its dendritic branches with graded membrane potentials; i.e. the voltages across the membranes can have continuous

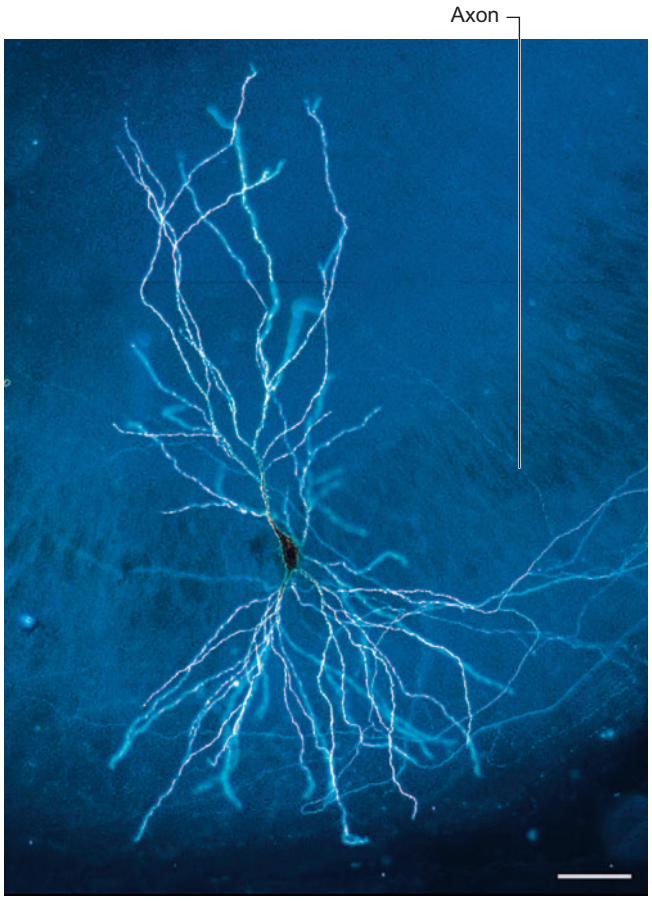


FIGURE 3.2 A single neuron. A spectacular recent photomicrograph of a single bipolar neuron. Cortical neurons may have ten thousand dendrites (input fibers) and one or more axons (output fibers). All fibers have smaller spines tipped with synapses connecting to neighboring neurons. The photo does not show the three-dimensional bushy shape of the neuron. *Source*: Standring, 2005.

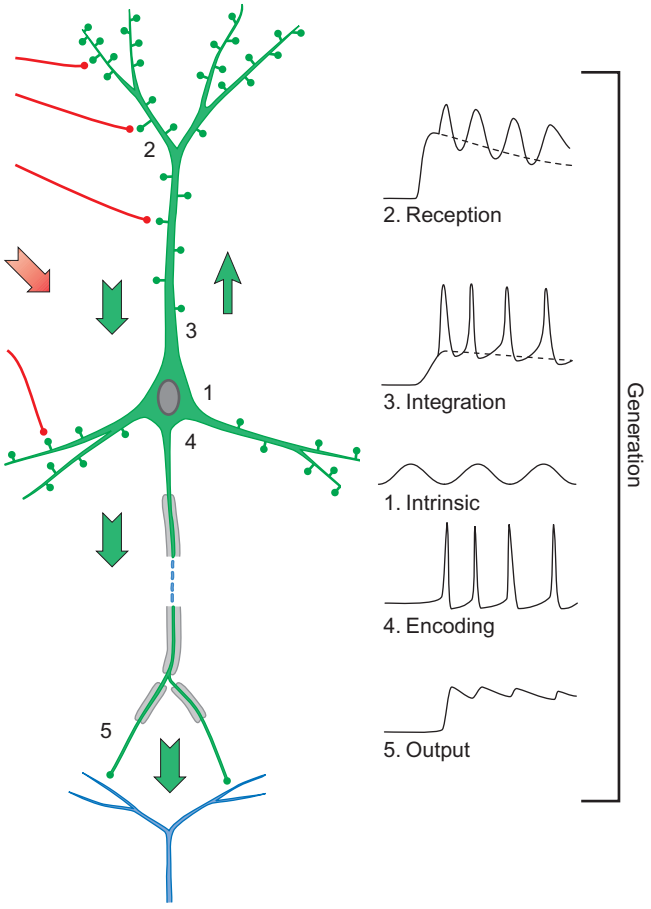


FIGURE 3.3 An idealized neuron. A simplified neuron with its dendrites on top, showing their spines as tiny knobs. Dendrites receive synaptic inputs that evoke graded membrane potentials (labeled Reception). When dendritic potentials rise above threshold in a very brief time interval (Integration), and are added to the intrinsic membrane potentials, they can trigger a fast depolarization of the axonal membrane – an all-or-none spike (Encoding). Spikes cause the release of neurochemicals at the axon terminals, which repeat the whole process, by evoking graded potentials in the next cell (Output). *Source*: Byrne and Roberts, 2004.

values. The graded dendritic potentials add up and, if the total voltage over a brief time interval exceeds about −50mV, they trigger a fast traveling spike or action potential in the axon of the nerve cell (see Figures 3.3 and 3.5).

The classical neuron is thought to send its signal by firing spikes – sending *action potentials* from the cell body down the axon to the terminal buttons. At the terminals, a neurochemical messenger is released to diffuse across a very small synaptic gap. It then triggers a postsynaptic potential in the neighboring neuron. Figures 3.3 to 3.5 show an abstract version of this process. In cognitive neuroscience, we usually focus on the ways neurons connect and interact in networks. The prototypical neuron is a useful starting point.

Given the complexity of the brain, our ideas for understanding it are basically simple. But simple units combine to make up massive nervous systems. There are many ways to use nerve cells for a host of different receptors, pathways, circuits, networks, and effectors.

1.2 Excitation and inhibition

Classical neurons are connected by way of synapses (Figure 3.6), which can be *excitatory* or *inhibitory*. Thus, the probability that the next neuron will fire a spike can be either increased or decreased. A neuron in cortex

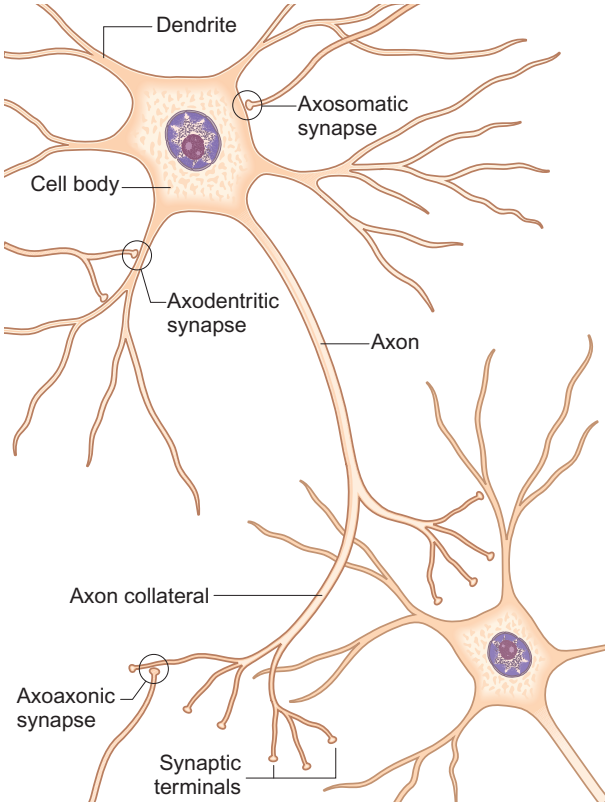


FIGURE 3.4 Two neurons connect across a synapse. Note that some synapses can feed back on the original neuron. *Source*: Byrne and Roberts, 2004.

may have some ten thousand input synapses, and a dozen output synapses terminating on other neurons. Dozens of other factors determine the activities of neurons – the sleep-waking cycle, the availability of chemicals for making neurotransmitters, and more. These factors all affect the likelihood of a signal going between two neurons, and they can be summarized as synaptic *weights*, which represent the chances that one neuron will cause the next one to fire. Thus, the great variety of neurons is often simplified into an idealized neuron, the integrate-and-fire unit; and the many ways in which neurons can trigger each other is simplified into connection probabilities between neurons.

Neurons have a great variety of shapes, branching patterns, and synapses. There are at least half a dozen major *neurotransmitters*, with at least thirty 'minor' ones, the neuropeptides. It is now known that electrical synapses, which use no neuro-transmitter at all, are much more common than was previously believed. Even the dendrites of a single nerve cell may be able to compute useful information. There is evidence that neuroglia, the support cells for neurons, may also have an information processing function. Other surprises keep coming. For example, for more than a century it was believed that unlike other body cells, new neurons were not produced after birth. However, it is now known that stem cells – new, undifferentiated progenitor cells

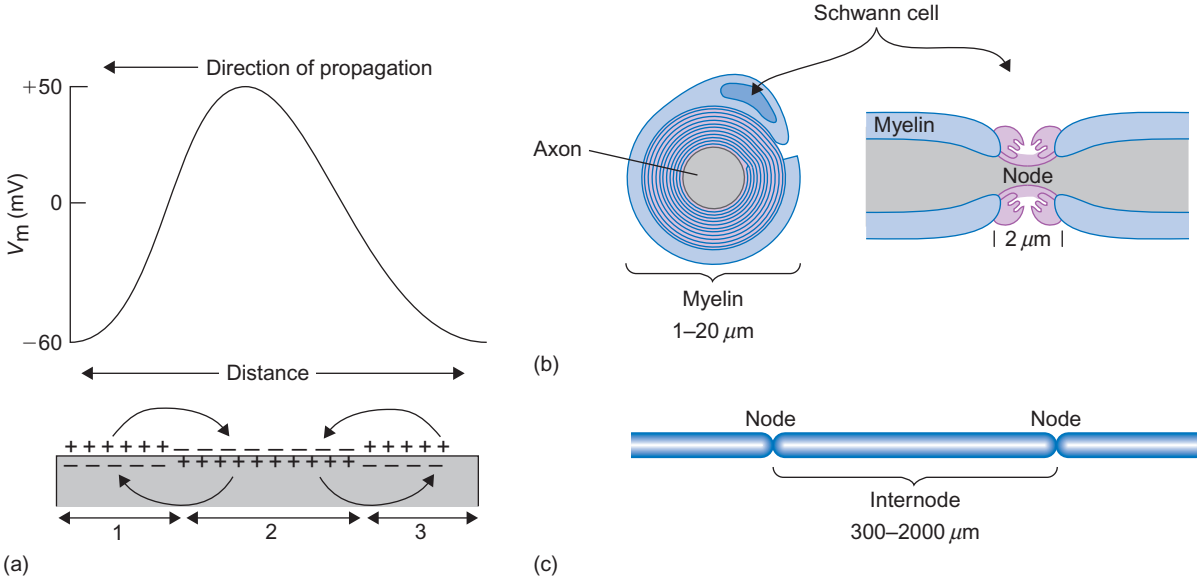


FIGURE 3.5 Signals traveling along the axon. (a) Neuronal signals travel along axons through the exchange of positive and negative ions in adjacent regions of membrane. In the axon, region 2 is undergoing depolarization, while region 3 has already generated the action potential and is now hyperpolarized. The action potential or spike will propagate further by depolarizing region 1. (b) Myelinated axons are wrapped in specialized Schwann cells. The axon is only exposed at the nodes of Ranvier. (c) Action potentials in myelinated fibers are regenerated at the nodes. Myelinated fibers have higher conduction velocity than bare axons. *Source*: Ramachandran, 2002.

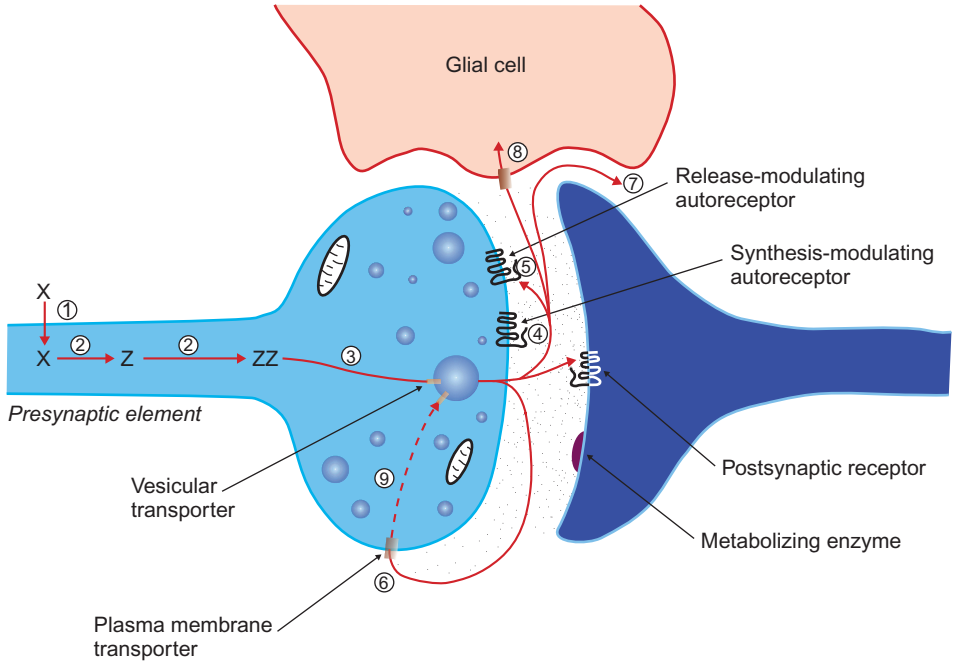


FIGURE 3.6 A basic synapse. Two cells in contact are labeled *presynaptic* (the lighter blue) and *postsynaptic* (darker blue). A spike in the presynaptic cell triggers release of a chemical neurotransmitter that diffuses across the synapse, and lowers the membrane potential of the postsynaptic cell. Some of the neurochemical machinery of this extraordinarily complex biological system is shown here. *Source*: Standring, 2005.

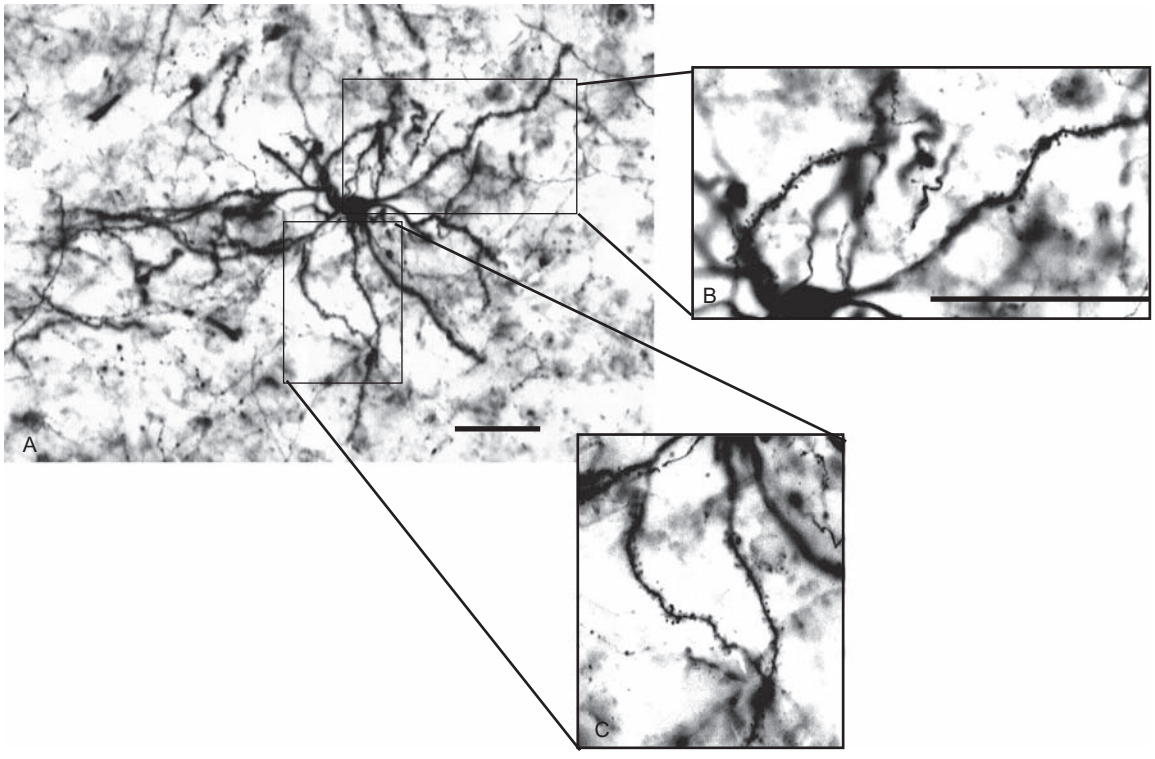


FIGURE 3.7 An actual photomicrograph of a single neuron in the basal ganglia. Notice the dendritic spines – tiny protrusions on the dendrites, often containing end buttons for synapses. The horizontal bars mark 50 micrometers. *Source*: Paxinos, 2004.

for neurons – are born in some parts of the adult brain. Synapses are known to grow throughout the adult lifetime, and small dendritic spines can grow in minutes to support new synapses (Figure 3.7). Thus, the standard neuron is only part of the whole picture. New evidence is bound to keep coming in for years to come.

As Shepherd writes (2004):

> The idea of the nerve cell as an independent cellular unit … continues to be one of the foundations of our concepts of nervous function. However, it has become clear that the whole neuron represents only one level in the organization of neural circuits and systems. We now recognize that nervous function arises out of many levels of organization, some of them within the neuron, some of them involving multineuronal interactions…

1.3 Neural computation

What justifies studying these simplified neurons? Perhaps more than anything else, it is the success of neural network models that have used simplified neurons in the last few decades. *Artificial neural nets* (ANNs) have been used to model many of the functions the brain performs – to recognize patterns, to plan actions in robots, learn new information, and use feedback to improve performance. Most ANN simulations are relatively small-scale and limited. None of them come close to the massive complexity of a living brain. But, for some jobs, ANNs have been more successful in doing human-like tasks than computer programs that use logic and standard mathematics. It is important to remember that ANNs *are* artificial. They are not the real thing, but they give us a greater understanding of the ways neural computation might work.

In the history of science, new mathematical techniques often help to understand new questions. Neural computation similarly helps to understand nervous systems. A great deal of progress has occurred on the basic mathematics of neural networks. There seems to be a small number of basic architectures – i.e. arrangements of simple units – with similarities to the networks found in the brain.

Cognitive neuroscientists commonly focus on *biologically plausible* neural net models, those that are based on the known properties of a specific set of neurons and their connections. However, artificial neural nets often provide useful approximations to the reality.

In addition to the simplified neuron of Figure 3.3, we will also use simplified synapses. As mentioned above, we will assume there are only two kinds of synaptic connections, excitatory ones (which increase the chance of triggering the next neuron), and inhibitory ones (which decrease that chance). *Glutamate*, the most common neurotransmitter in the brain, is known to be excitatory. *GABA* (gamma-amino butyric acid) is the most common inhibitory neurotransmitter. So our simplification is a part of neural reality.

2.0 WORKING ASSUMPTIONS

We have discussed using simple and idealized neurons in order to describe the basics of neural firing and connectivity. We will use these basic ideas already laid out as working assumptions as we continue our discussion of neurons and their connections. To summarize our working assumptions, they are:

1. The *integrate-and-fire neuron*. We will assume that neurons work by adding graded voltage inputs until the total membrane voltage on the target neuron goes past a threshold value (approximately −50 mV in real neurons). If it does, an all-or-none spike fires down the output branch, the axon.
2. Connections are either *excitatory* or *inhibitory*. We can therefore assign a single number to the probability that neuron A will trigger neuron B. That number is called the *weight* of the connection. As probabilities, connection weights have numbers between −1 and +1. Plus 1 means a 100 per cent certainty of triggering the next neuronal spike, and −1 is 100 per cent certainty of stopping the next neuron from firing. Weighting schemes can be more complex, but this is a useful first approximation. The vastly complicated neurochemistry can be reduced to just one number for the probability of transmission, the 'weight' of each connection.
3. A second reason for the simplified neuron and synapse is that the basic mathematics of networks appears to be very successful in simulating cognitive functions. *Neural nets* can simulate the kind of pattern recognition that sensory systems perform, although our models are much simpler than any brain mechanism known today. Neural nets can learn and store information in much the way real neurons are believed to. Since the basic types of ANNs were worked out in detail over the last several

decades, they have been applied to many practical uses, from computer-based face recognition to predicting the stock market. That is also scientifically important, because it shows that we understand enough about networks to begin to see how the brain might do those things. As always, we must be prepared to see the limits of our knowledge; but we have a basis for departure.

4 Neurons can form one-way pathways, such as the optic nerve to the visual thalamus (the lateral geniculate nucleus). However, one-way pathways are quite rare. More likely, neurons run in two directions, forming two-directional pathways and networks, in which activity at point A triggers activity at point B, and vice versa. This is often called *re-entrant connectivity* (Edelman, 1989).

5 As we will see, the nervous system loves *arrays* of neurons, often called *maps*. The cerebral cortex is a massive six-layer array, with an estimated ten billion cells and trillions of synaptic connections between them. The retina at the back of the eye is another array, this time with three layers (see Chapter 6). In fact, *all* sensory surfaces are arrays of receptors and their closely linked layers of relay and processing cells. Other arrays are found in the sensory thalamic nuclei, in the superior colliculi (which control eye movements), and in arrays of cells that control muscles. The brain's liking for arrays and maps, with dense connections between them, is another useful working assumption.

6 *Hebbian cell assemblies*: when neurons combine by triggering other neurons, the resulting pattern of activity may be stable or unstable. Unstable patterns tend to die out, while stable patterns remain for some period of time. Such stable patterns are often called *cell assemblies*, and the term 'cell assembly' is often attributed to Donald O. Hebb (Hebb, 1949). Hebbian cell assemblies may involve neighboring cells, or they may involve cells that are far away from each other. Cell assemblies that combine both excitatory and inhibitory connections tend to be more stable and lasting, as we will see. In the brain, transient connections are thought to be mainly electrochemical, while more lasting ones are thought to require protein synthesis.

2.1 Starting simple: receptors, pathways, and circuits

While reflex circuits can be triggered by outside stimuli, they are normally integrated seamlessly into voluntary, goal-directed activities. For example, you can turn your head from side to side while reading this sentence. That is, you can follow a voluntary goal (stated in the previous sentence), and your oculomotor system will still keep your eyes focused on the moving window of the words you are reading at this instant in time. It is a remarkable achievement of sensorimotor adaptation, and most of the time it is quite unconscious and automatic. Oculomotor coordination is not just a simple reflex arc.

Voluntary brain mechanisms, guided by explicit goals, are associated with cortex in humans. Very sophisticated subcortical circuitry is also engaged in planning and executing actions. Spinal centers may carry out commands from higher centers using sensorimotor reflexes, but they also return feedback signals to the brain. All these levels of control have *endogenous* (internal) as well as *exogenous* (sensory) input, both conscious and unconscious (Goodale and Milner, 1992). Thus, while there are certainly some simple reflex circuits like the famous knee-jerk reflex in Figure 3.8, reflexes rarely work in isolation. They normally work in the service of cortical goals.

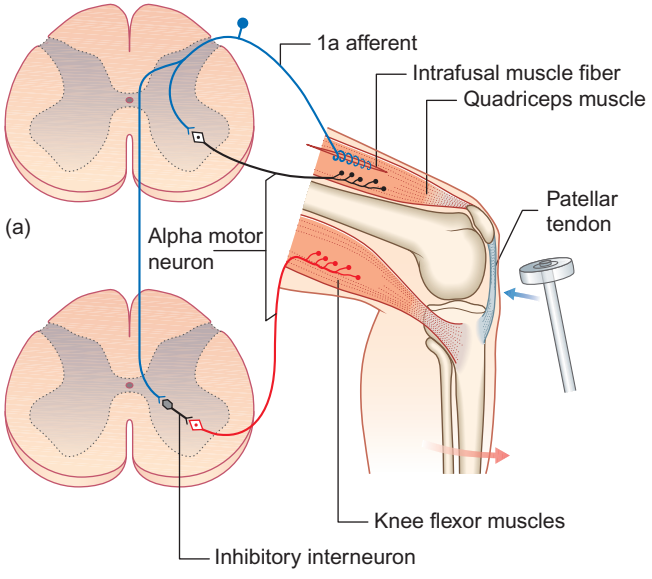


FIGURE 3.8 A simple reflex circuit. If you drape one leg over the other and tap just below the kneecap, your lower leg will jump out. This is the famous knee-jerk reflex, technically called the patellar tendon reflex. It is a classical example of a spinal reflex, controlled by a simple circuit. Sensory neurons pick up the mechanical tap, and transform it into a neural signal which is sent to the spinal cord. There, an interneuron links the sensory impulses to motor neurons, which contract the muscles in the upper thigh, making the lower leg jump outward. *Source*: Standring, 2005.

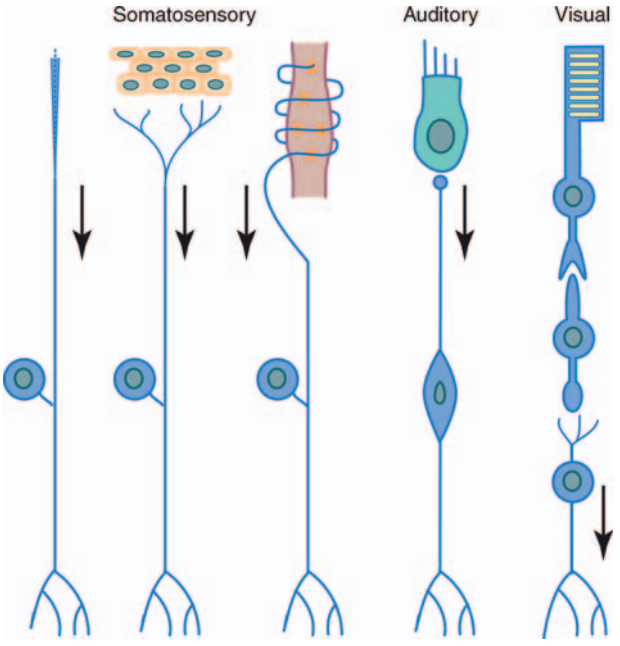


FIGURE 3.9 Receptors transform external energy patterns into neuronal activity. Although these receptors belong to different sensory systems, they are similar in structure and function. All convert physical energy from the environment into neural signals. *Source*: Hendry *et al.* in Squire *et al.*, 2003.

Reflexes are innate circuits. They emerge during normal development and some disappear after some time, like a baby's innate grasping reflex, which allows it to take strong hold of an adult's finger. But *learned* nonvoluntary processes are not reflexes. They are complex, interactive routines called *automatic processes* – highly practiced skills and habits. For example, as a skilled reader you automatically process the difference between the letters 'b' and 'p', even though they may look similar to non-readers. In speaking and typing, your muscle control is very fast, highly organized, and mostly unconscious. Humans use numerous automatic processes to carry out normal actions. Such learned automatisms are typically unconscious, effortless, and not under detailed voluntary guidance. They should not be confused with reflexes. Automatic skills start out under cortical control, but after sufficient practice they tend to come under subcortical control (Haier *et al.*, 1992; Chein and Schneider, 2005).

Each sensory nerve may actually contain parallel channels, conveying somewhat different features of the world. Thus, vision has a color pathway called parvo-cellular (because it has somewhat smaller cells), and a separate bundle of 'black and white' neurons called magnocellular (meaning small cells) (Figure 3.9). Similarly, the somatosensory pathway combines parallel channels for light touch, for heat, pain, and so on.

Most sensory nerves stop off at the thalamus, where they contact synaptic relays on their way to cortex (Figures 3.10 and 3.11). These thalamic nuclei provide point-to-point connections. Vision and touch are *topographically* organized, projecting receptor maps into higher level maps, well into the cortex. Audition tends to be more *tonotopically* organized, with neuron arrays corresponding to sound frequencies.

Most sensory and motor pathways split and cross over the midline of the body on their way from the periphery to cortex. The evolutionary reason for crossover is still mysterious, but it is a pervasive feature in humans and other mammals.

While we tend to think of input-output pathways as carrying one-way signal traffic, this is actually rare. Most pathways run in both directions. For example, while there is a one-way flow of signals from the retina to the visual thalamus, the next stage goes in both directions. Thus going from thalamus to V1, about 90 per cent of the neurons are running the wrong way (i.e. from V1 *downward* to the visual thalamus)! In the auditory system, the downward flow of neural signals goes to the very receptors themselves (see Chapter 5).

This two-way signal traffic means that much of the central nervous system should be viewed not as simple traffic arteries, but as re-entrant loops – equivalent to neural networks with two or more layers (Figure 3.11). Edelman (1989) and colleagues have particularly emphasized re-entrant processing as a basic feature of the brain. From this point of view the brain is a vast collection of mutually echoing maps and arrays.

2.1.1 Receptive fields and lateral interactions

Lateral inhibition was first proposed as a hypothesis by Ernst Mach, a German physicist in the 1860s, based on the tendency of continuous visual gradients to be perceived as discontinuous. It was a brilliant hypothesis that has since been confirmed by directed testing (Figure 3.12). Lateral inhibition seems to be used in many places in the brain (Figure 3.13). In the retina, neighboring cells can inhibit each other, so that a tiny point of light on one cell will tend to stand out in contrast to the adjacent ones (Figure 3.14). In touch, neighboring cells in the skin also use lateral inhibition. At higher levels in the brain, similar semantic concepts may have the effect of inhibiting each other, so that 'astronomy' and 'astrology' might not be confused. Like the other neural strategies discussed in this chapter, the

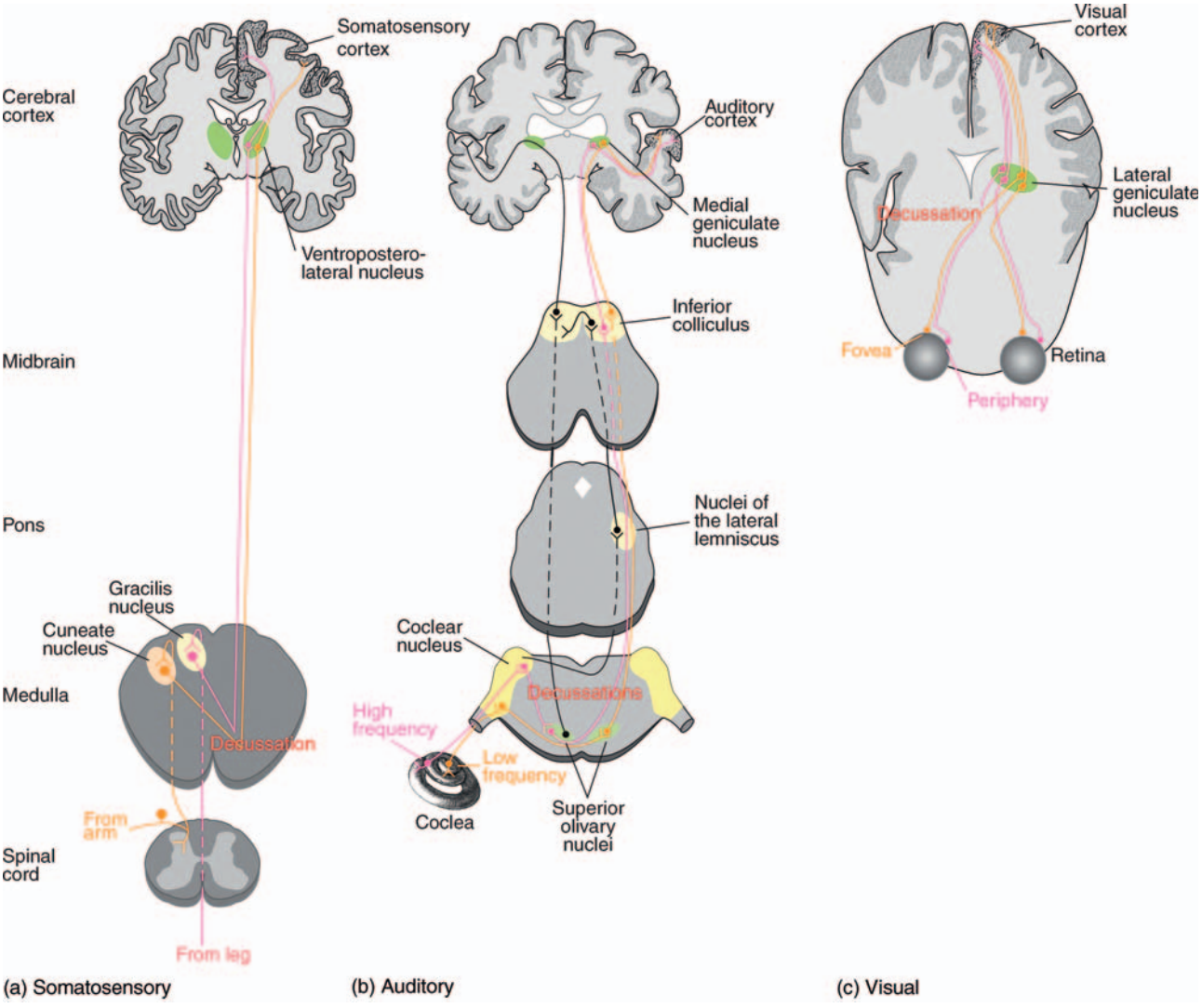


FIGURE 3.10 Similarities between sensory pathways: body senses, hearing, and vision. All the senses begin with arrays of receptors, like the layers of touch receptors of the skin and the array of light receptors of the eye. After local processing, sensory information is condensed into a single nerve pathway, a compact bundle of neurons, which carries sensory signals to cortex. Note that these three sensory pathways stop off in thalamic relay nuclei, marked in green. All three pathways also split and cross over to the opposite side on their way to the cortex, called *decussation. Source*: Hendry *et al.* in Squire *et al.*, 2003, Elsevier.

brain often borrows successful tricks and tips from an earlier evolutionary form and may translate it into later adaptations.

3.0 ARRAYS AND MAPS

As we have pointed out, neuronal *arrays* are widely found in the brain. An array is a two dimensional grid of neurons. When arrays represent a spatial pattern, they are often called *maps*. Spatial maps are a form of spatial coding in neurons. The brain performs temporal as well as spatial coding, and may have a number of other ways of representing and processing information. Nevertheless, spatial maps are the most obvious kind of neural code (Figures 3.15 and 3.16).

The retina itself can be thought of as a three-layered map of light receptors and their neighboring neurons, including ganglion cells, which send their axons from the retina to the visual relay cells of the thalamus (the lateral geniculate nucleus) (see Chapter 6). The thalamic visual cells then project their fibers to the first visual area of the cortex, area V1 of the occipital lobe.

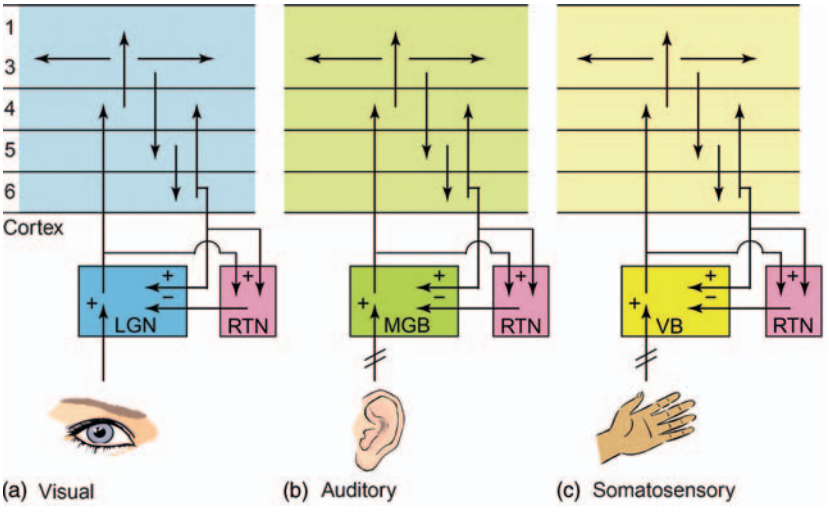


FIGURE 3.11 Sensory regions interact with thalamic nuclei. The thalamus is often called the 'hub' of the brain. It is not the only hub, but perhaps the most important. Notice that vision, hearing, and touch pathways all stop off in the thalamus on their way to their cortical projection regions. However, information is constantly bounced back from the cortex to various thalamic nuclei, so that there is a constant flow of signaling between all parts of cortex and thalamic nuclei. In some cases, the thalamus amplifies cortical activity, while in others it blocks or inhibits it. Note the striking similarities between cortical input and output layers in these three senses. *Source*: Alitto and Ursey, 2003.

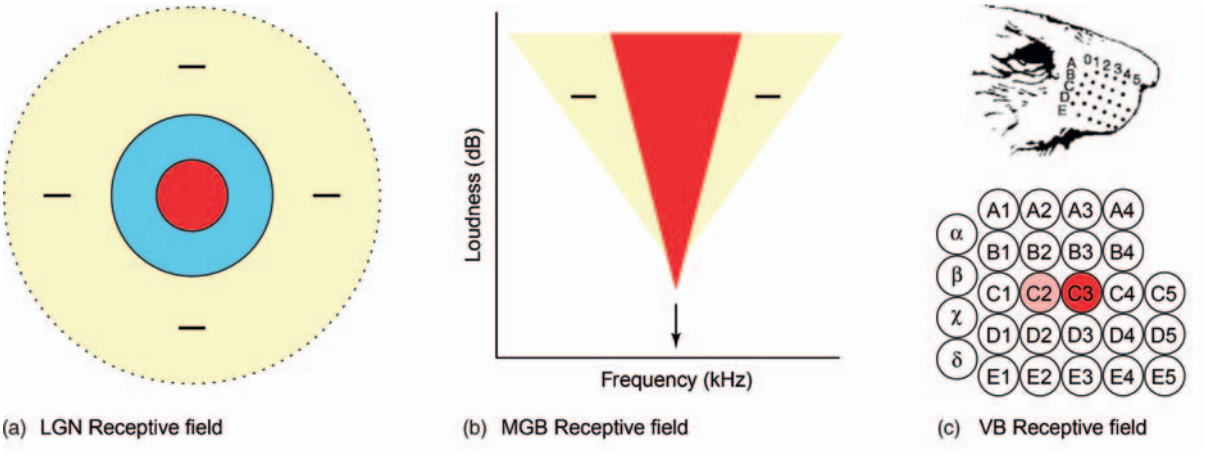


FIGURE 3.12 Lateral interactions. The brain often uses the same strategy in many different places. On the left is a 'center surround' cell of the visual thalamus (the lateral geniculate nucleus). Light falls on the red circle in the middle but no light falls in the surrounding ring. Neurons pick up both light input and the absence of surrounding light, and enhance the contrast by mutual inhibition in the same layer, called lateral inhibition. The same mechanism is used in the center image, and even in the barrel cortex of the rat, the place in cortex where its whiskers project their neurons in a very simple, one-to-one fashion. Barrel cortex is often used to study cortical processing for this reason. Adjacent whiskers also show lateral inhibition, which is also found in touch, hearing, and even attentional control in the human brain. *Source*: Alitto and Ursey, 2003.

V1 also looks like a detailed map of the visual input, with different quadrants of the visual field projected to different parts of this region. From area V1, most of the visual information projects to other 'maps' in the cortex, some of them in the visual cortex itself, but also beyond it. While the resolution of spatial details tends to blur after V1, higher-level visual maps respond to more complex and abstract stimuli, like faces, objects,

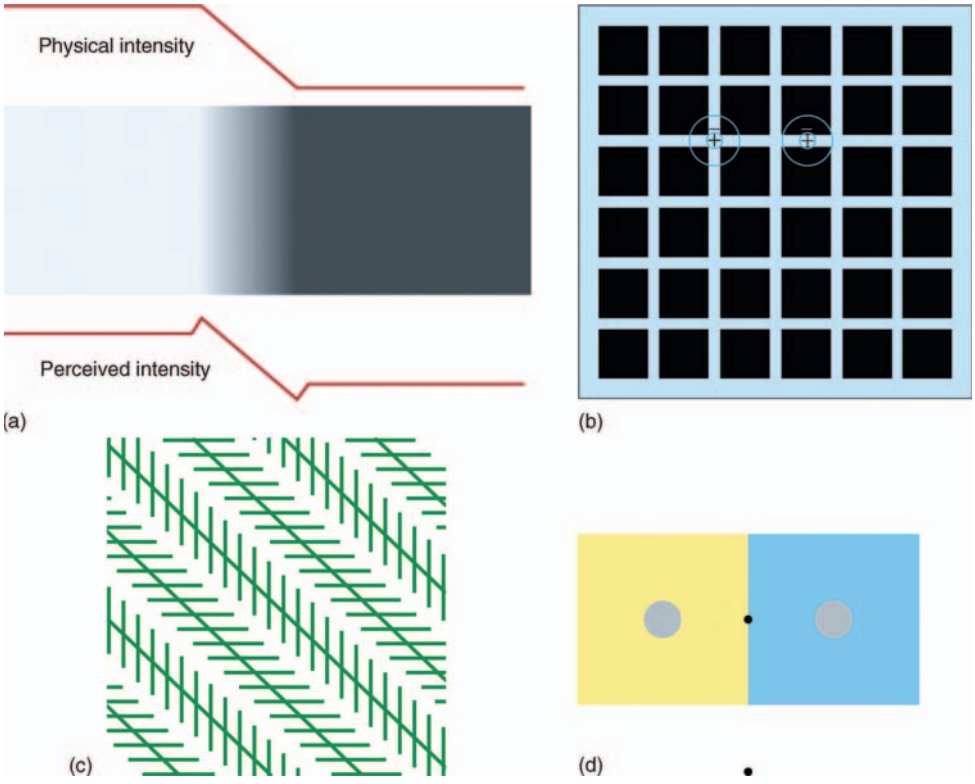


FIGURE 3.13 Visual demonstrations of lateral inhibition. Lateral inhibition was first proposed as a hypothesis by Ernst Mach, a German physicist in the 1860s, based on the tendency of continuous visual gradients to be perceived as discontinuous. It was a brilliant hypothesis that has since been confirmed by directed testing. Notice that lateral inhibition also applies to adjacent black squares, to color perception between opponent colors, and even to the perception of 'train tracks stimuli' which signal spatial depth to the brain. *Source*: Eagleman, 2001.

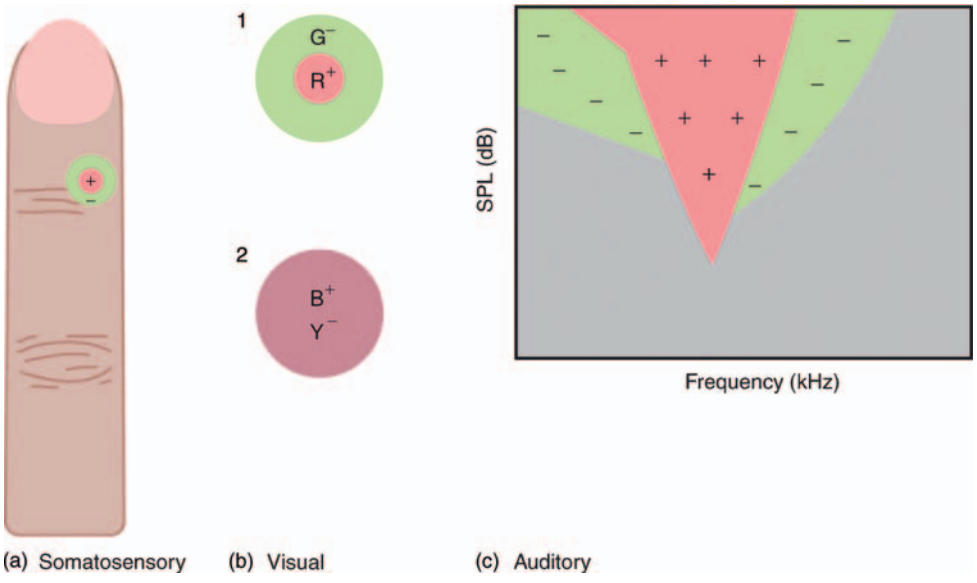


FIGURE 3.14 Center-surround receptive fields in sensory cortex. Mapping of somatosensory (tactile), visual, and hearing space is accomplished in part by neurons with center-surround receptive fields that are sensitive to specific aspects (location, color, frequency) of a sensory stimulus.

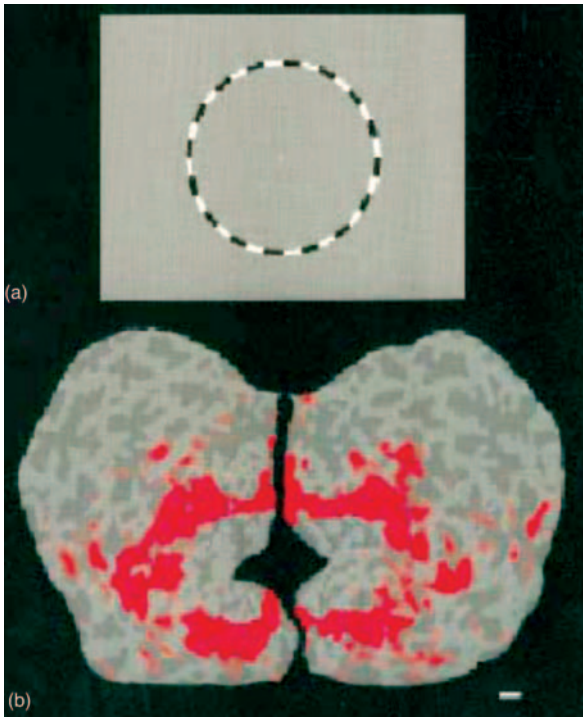


FIGURE 3.15 The visual input projects to cortical areas. In a classic experiment, Tootell *et al.* (1996) showed that a circle around the center of visual fixation evokes corresponding activity in the first visual projection area, Area V1. The authors made use of the fact that V1 expresses a topographical visual input, and that circles are symmetrical around the fixation point. We are looking at a flattened projection of area V1. *Source*: Tootell *et al.*, 1996.

visual scenes, attentional, emotional, and perhaps even decision-making networks, as they work their way forward in the cortex (Figure 3.17). Thus vision involves what looks like a large and widespread set of maps of the light input to the eyes. While this view

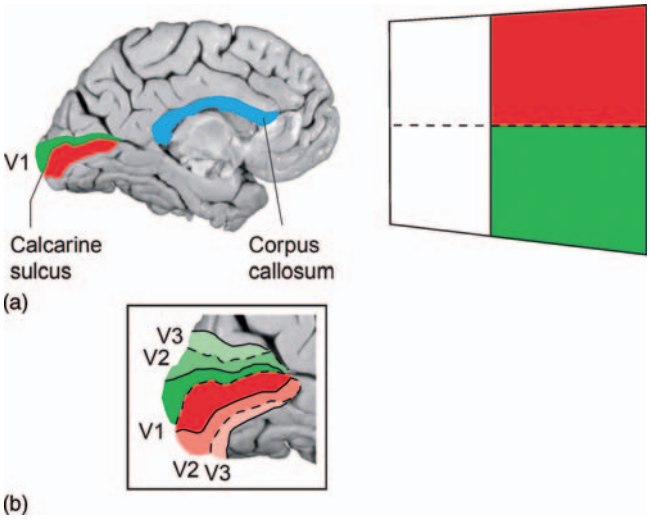


FIGURE 3.16 Visual quadrants map to cortical quadrants. Notice that the first visual projection area V1 represents different visual quadrants in different regions of cortex. The bottom right quadrant projects into V1 in the left hemisphere, in the upper half of V1. The early visual areas are folded tightly into the occipital cortex, around a fold called the calcarine sulcus. *Source*: Zeki, 2003.

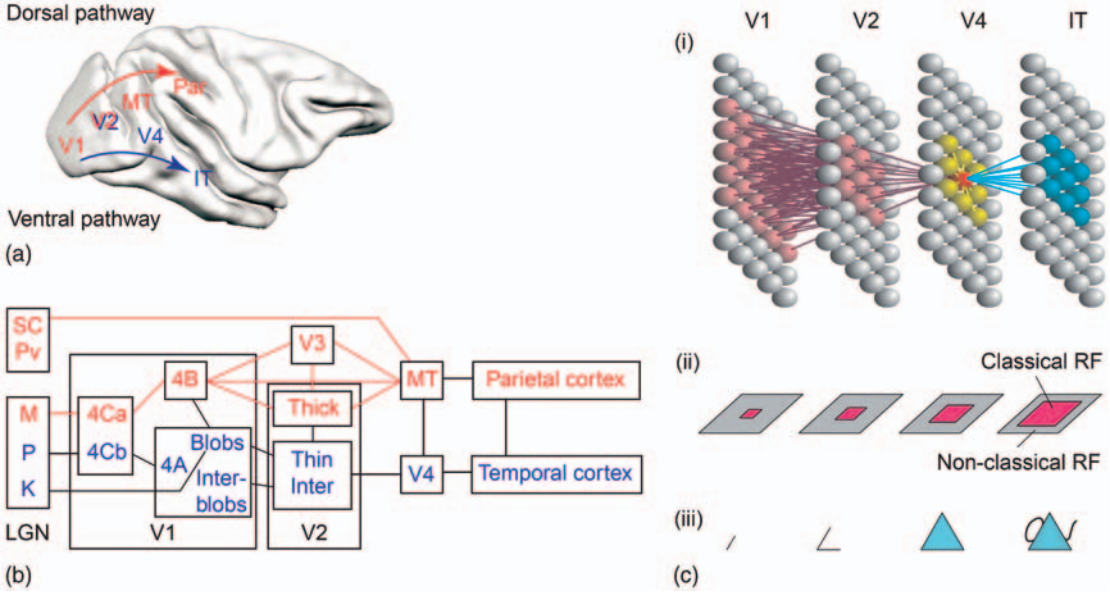


FIGURE 3.17 Visual maps in the macaque. The rhesus macaque monkey's visual brain is often studied because of its similarities to the human visual brain. On the left are the major visual pathways in the macaque cortex. Each one flows from topographical map to topographical map. Starting with area V1, the information flows to later 'V' areas while preserving the topography of the input. The upper pathway is sensitive to location, and is therefore called the 'Where' pathway. The lower pathway is sensitive to color, shape, contrast, and object identity, and is called the 'What' pathway. It is believed that activity in the 'What' pathway is directly involved in conscious visual experiences, perhaps beginning in the object recognition area (IT). The 'Where' pathway may provide spatial frameworks for the 'What' pathway. It may not be directly conscious, but it shapes the perceived location of objects. (RF = receptive field.) *Source*: Lamme and Roelfsma, 2000.

is undoubtedly too simple, it captures a good deal of evidence.

The body senses, like touch and pain perception, also project to map-like regions of cortex. Other senses like hearing, smell, and taste are less spatial in nature, but the auditory cortex has map-like regions organized by pitch, like the strings of a harp. Thus, even the non-spatial senses show regular neuronal arrays and map-like regions. Finally, information from specific sensory systems is combined in the parietal cortex, using spatial arrays that combine auditory, visual, touch information into map-like regions. These include a body-centered map (called egocentric) and an object-centered spatial array (called allocentric). It seems as if our brains like to organize a vast amount of incoming information in arrays that mirror the layout of the spatial surroundings. And motor cortex, as you might guess, looks much like a distorted map of the output systems, the skeletal muscles of the body (see Chapter 5).

It is tempting to think that with the sensory half of cortex (the posterior half) using so many maps, there must be a little person inside looking at the maps. But this is the 'homunculus fallacy', as philosophers call it. The trouble with this idea is that it explains nothing, but merely moves the question to another level: Does the homunculus have its own brain, with its own spatial maps, and another, even tinier homunculus sitting inside?

The question for scientists is therefore how to make sense of the great number of spatial and other neuronal arrays in the brain without resorting to the fallacy of supposing that we all have a little creature inside, looking at all the neuronal maps. Neural network models provide one set of answers today, as we will see.

3.1 Maps flow into other maps

The nervous system often uses layers of neurons in giant arrays; indeed, the entire cortex is a massive six-layered array containing about ten billion nerve cells. Neuronal hierarchies are stacked arrays of nerve cells.

3.2 Neuronal arrays usually have two-way connections

There is one very important surprise in this tidy picture of maps flowing into higher-level maps of the visual input: after the thalamic nucleus, most axons run *downward* from cortex to the thalamus. Some 90 per cent of the axons between LGN (lateral geniculate nucleus) and V1 send spikes downward to LGN, rather than upward to V3. Higher up, there is always two-way traffic of signals between V1 and V2, V2 and V3, and onward. This might seem pretty odd for a simple transmission idea of the visual pathway. But we will see that bi-directional flow of spikes is the norm in the brain, not the exception (Figure 3.18). There are very few one-way streets in cortex. This is a very important point, which compels us to think of neuronal signals in a richer way. We will explore two-way transmission in more detail below. Receptive fields of sensory neurons become larger and more complex as we go up in the visual hierarchy.

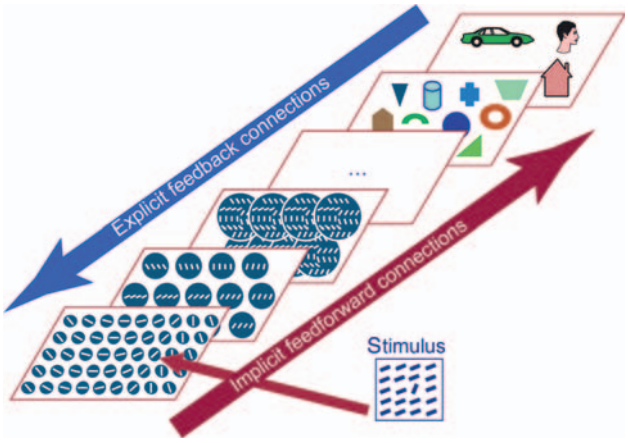


FIGURE 3.18 Two-way traffic between arrays. Two-way traffic is the norm in the brain. For that reason, it makes more sense to think of the arrays of visual regions as layers of a two-way network, rather than one-way paths from point to point. Notice that lower maps are sensitive to simpler stimuli, while higher ones show faces and cars. However, there is constant predictive flow of information from higher to lower maps, to make it easier to identify all levels of description. *Source*: Ahissar and Hochstein, 2004.

3.3 Sensory and motor systems work together

Finally, while there are very clear anatomical divisions between sensory and motor pathways, they are constantly interacting. When we speak, we also hear ourselves speak. When we walk, an array of visual information streams across our retina. Video games that simulate the flow of optical vistas really given a sense of motion, even though they are only visual. The brain is constantly updating its motor systems by means of sensory input, and telling the sensory systems what to expect by way of motor signals.

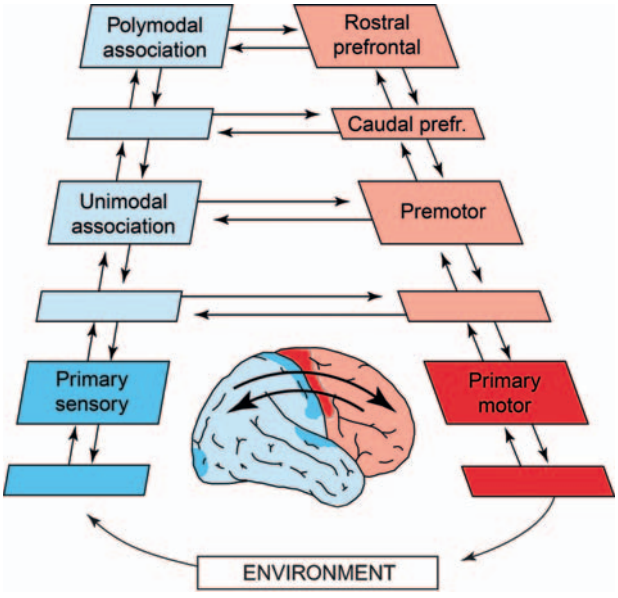


FIGURE 3.19 Sensory and motor hierarchies are themselves arranged in hierarchies. Fuster (2004) suggests that all of cortex can be seen in terms of cycling sensory and motor hierarchies, with information flowing between the posterior (sensory) regions and the frontal (motor and planning) areas. Early sensory cortex flows into unimodal association areas, which interact with premotor cortex, which is believed to encode the 'urge' to perform an action. Higher up the sensory hierarchy, polymodal association areas combine hearing, touch, and vision, and interact with the forward part of the pre-frontal cortex. Notice that there is constant exchange of information through the environment as well. Thus, we can hear ourselves speaking, and we can see a flow of visual vistas when we walk. *Source*: Fuster, 2004.

FIGURE 3.20 A step pyramid as a hierarchy. One useful image for a brain hierarchy is a step pyramid, like the Inca city of Machu Picchu. While the levels are stacked on top of each other, signaling can take place through many different pathways in the hierarchy. Thus, the people exploring the step pyramid can walk up, down, or sideways.

Fuster's classical diagram of the cortex makes this point emphatically (Figure 3.19). Functionally, the nervous system is always cycling information between input and output channels, to keep the sensory and motor world in synchrony (Fuster, 2004; Kandel *et al.*, 2004).

Fuster (2004) suggests that both front and back can be viewed as massive hierarchies of local hierarchies, starting from sensory receptors, and becoming more and more general as information flows upward in the sensory hierarchy (see Figure 3.19). The motor hierarchy can be viewed as going in the opposite direction, ending up at motor neurons. However, as the diagram indicates, more and more information is exchanged between the two hierarchies in an ongoing perception-action cycle, from a low level (as in listening to one's own voice speaking) to a very high level of planning, thinking, and anticipating the future (see Figure 3.20 for an image of an architectural hierarchy).

Friston (2003) has published a useful diagram for a processing hierarchy (Figure 3.21), which we will adopt here. Each neuronal array is called a 'map' in this version, and while maps exist at different levels, signals may travel up, down, and laterally. We will see some examples in later chapters.

Notice that neural net models sometimes use different directional names to refer to the same idea. 'Bottom up' is the same as 'feedforward'. 'Top-down' flow is often called 'feedback'. We can simply flip the hierarchy on its right side to make 'bottom up' look like 'feedforward'.

3.4 Temporal codes: spiking patterns and brain rhythms

Arrays, maps, and hierarchies support *spatial* coding in neurons. But the brain makes use of *temporal* coding

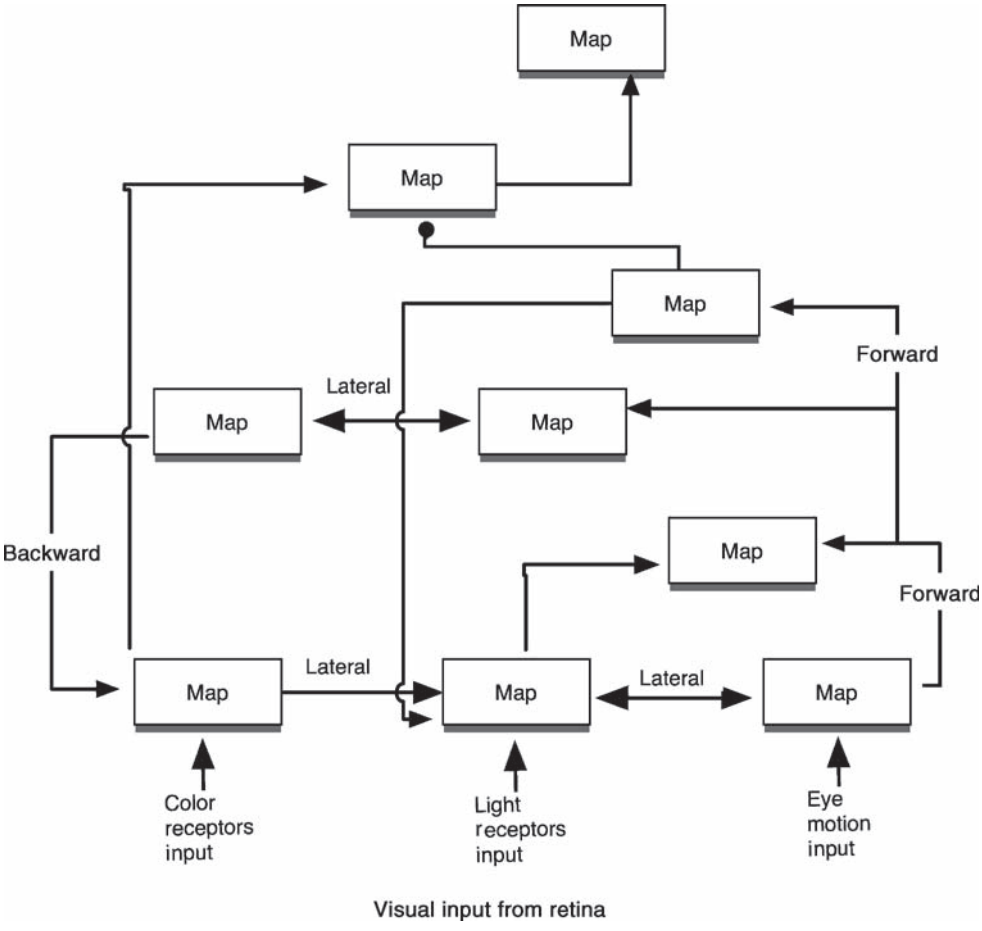


FIGURE 3.21 An abstract hierarchy. Notice that like the step pyramid above, this hierarchy allows information to flow in all directions. This is a typical layout for sensory and motor hierarchies. *Source*: Friston, 2003, redrawn.

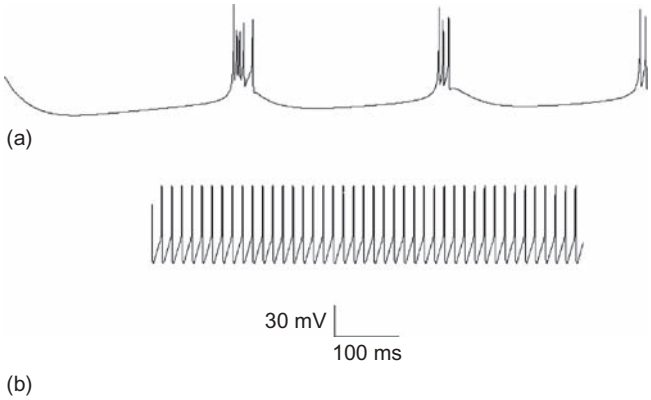


FIGURE 3.22 Neurons have different spiking codes. While it is easy to visualize the map-like spatial coding in the brain, neurons also code information over time. The two electrical traces show the voltages of simulated thalamic neurons. These neurons have two different spiking codes (McCormack and Huguenard, 1992). *Source*: White, 2002 in Ramachandran, 2002.

as well. Figure 3.22 shows an example of a single neuron in the thalamus which shows two different spiking patterns. The timing of a neuronal spike relative to other neurons can also convey information, much as a clock shows the time of the present moment relative to the 24-hour cycle. Neurons like this may serve as pacemakers for large populations of cortical neurons during delta sleep, for example (Figure 3.23). Another hypothesis suggests that fast firing of thalamic neurons may trigger waking when the sound of a loud noise or a crying baby is detected, or some other significant stimulus. Arboreal primates, for example, need to respond very quickly if a tree branch breaks.

Individual neurons also exhibit *spiking codes*. For example, the auditory nerve performs frequency coding (see Chapter 5). Every time the eardrum vibrates,

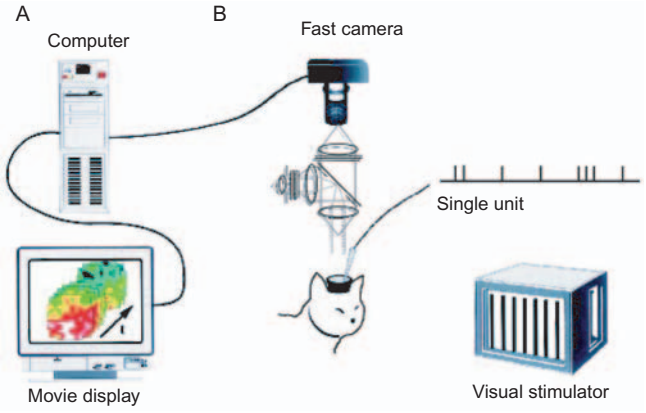


FIGURE 3.23 How single neurons are recorded in living animals. The needle electrode causes no pain, since the brain itself has no pain receptors. It is implanted using a scalp attachment that allows the cat to move comfortably. The electrode picks up 'spikes' from a single neuron, which are amplified and shown on the upper right. Trials over time are shown on the colored screen. *Source*: Tsodyks *et al.*, 1999.

three tiny bones in the inner ear transfer mechanical ripples to a fluid, which in turn moves hair cells on the basilar membrane. The hair cells are the auditory receptors, which fire whenever they are mechanically stimulated. Together their axons make up the auditory nerve and, so long as the incoming sound frequency is fairly low, the firing rate of the auditory nerve follows the movements of the eardrum. The auditory nerve therefore shows a simple one-to-one frequency code. It is a temporal code rather than a spatial map of input (see Section 3.5).

When we look at the electrical activity of tens of billions of neurons, the entire brain seems more like an orchestra than like a single piccolo. After hundreds of millions of years of evolution, it seems likely that the brain has evolved neurons with many kinds of temporal and spatial codes.

BOX 3.1 Some ways to visualize neural communication

Neuronal communication can be visualized using standard graphics.

Figure 3.24(a) shows a *cross-correlogram* reflecting the activity of one neuron depending on a related one. Sherman and Guillery (1985) recorded spikes from a target neuron (postsynaptic) when a spike occurred in an input neuron (presynaptic). We are therefore looking at the efficiency of spike signaling across a synapse. Sherman and Guillery recorded in a part of the brain where a one-to-one relationship can be found between two neighboring neurons. The presynaptic cell is located in the visual thalamus, which relates point-to-point to cells in the primary visual cortex, area V1 (see Chapter 6).

The vertical axis indicates the number of spikes in the postsynaptic neuron, given a previous spike in the presynaptic neuron at time t = 0. Most neurons show a constant background rate of firing, so that we are looking for activity that is significantly *above* the background rate. In this example the activity of the two neurons is very closely linked. Within a few milliseconds after the presynaptic neuron fires, the corresponding postsynaptic cell also fires. We are therefore seeing high-fidelity transmission of a spike signal across a synapse.

Figure 3.24(a) is the simplest example of how two neurons can covary. They often interact in much more complex ways, of course. Cross-correlograms can be calculated between any pair of neurons that can be recorded.

Figure 3.24(b) shows that neural communication can be observed on the scale of the entire brain. In this case we are looking downward at the cortex displayed as a circular disk, with the eyes and the nose of the subject on top of the circle. The black lines represent gamma synchrony between the connected points, as recorded by intracranial electrodes. (Intracranial recording often is done in conscious epileptic patients before surgery.) Gamma rhythms are defined as brain rhythms in the EEG band between 25 and 120 Hz.

Doesburg *et al*. (2007) presented visual flashes to the left and right of the visual fixation point in conscious epileptic patients. Figure 3.24(b) shows the case of a visual cue presented on the left side of the visual field. Because of the cross-wiring of the visual pathway, a left visual cue triggers activity in the right occipital cortex, where visual signals are detected and identified. The occipital cortex thereupon generates gamma activity that seems to recruit resonant "echoing" in many other parts of the cortex, as shown by high gamma synchrony between distant regions. Such task-related synchrony now has been found in many cognitive tasks (see Chapter 8).

Finally, Figure 3.24(c) shows *time-frequency graphs* of brain activity after a visual face is presented, obtained by Lachaux *et al*. (2007), again using MEG and intracranial recording in the lateral occipital gyrus, a part of the visual cortex. In these graphs the vertical axis represents brainwave frequency, and the horizontal axis shows the time in milliseconds after some event of interest, like the presentation of a face. The colors in the color bar represent the intensity of electrical activity (called power), with white and yellow representing the highest levels.

As you can see, there is a marked burst of high power beginning almost immediately after time t = 0. The frequency range of the yellow and white burst is 50–150 Hz

on the vertical axis, and about 100–500 milliseconds after the onset of the visual stimulus. Time-frequency graphs are used widely in cognitive neuroscience, and it is important to understand them.

The black marks at the bottom of Figure 3.24(c) indicate a decrease of power in the alpha band of 8–12 Hz. Decreased alpha often is seen in visual tasks.

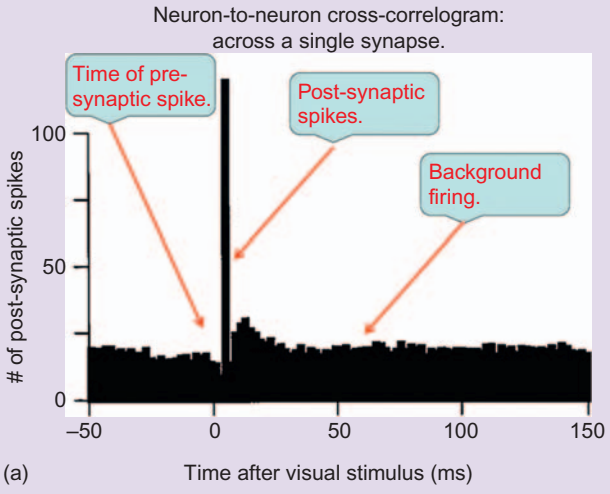


FIGURE 3.24(a) A cross-correlogram relating the firing of a thalamic neuron to the corresponding neuron in the visual cortex. *Source*: Adapted from Sherman and Guillery, 1998, with permission.

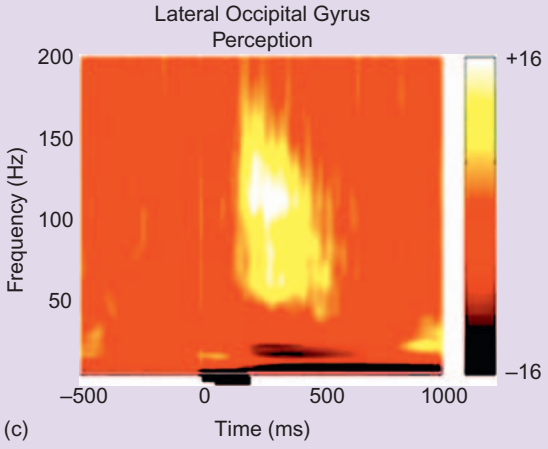


FIGURE 3.24(c) A time-frequency graph used to display the results of neuronal signaling studies in the brain. It allows us to see a frequency range of electromagnetic activity over a precise time period after a stimulus is presented, with colors indicating the intensity of the activity. This graph shows a high power burst (white and yellow colors) in the gamma range (about 50–150 Hz in this case), beginning about 100 ms after the onset of the face presentation, and dropping rapidly after ~500 ms. The dark traces along the bottom of the graph indicate a loss of signal power in the theta and alpha range of 4–12 Hz for about a second. The horizontal black bar below the graph shows the duration of the visual stimulus, a "mooney face" (Chapter 8). *Source*: Lachaux, J. P., *et al*., 2007.

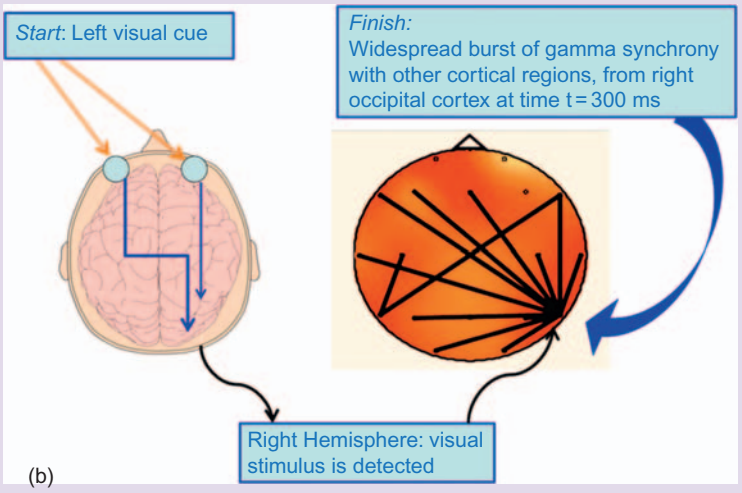


FIGURE 3.24(b) A top-down head view of intracranial EEG in response to a visual cue in the left visual field. The left image shows the path taken by neuronal signals corresponding to the visual cue in the left visual field. Notice the dark lines on the image of the head (right) showing high gamma synchrony between visual cortex and other cortical regions, both in the same and opposite halves of the cortex. Gamma synchrony seems to play a role in cross-regional signaling in many cognitive tasks. *Source*: Adapted from Doesburg *et al*., 2007, with permission.

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3.5 Choice-points in the flow of information

If the brain had only straight highways it would be easy to understand. Instead, it has pathways with many choice-points, in which traffic can flow right or left, or jump a whole level forward or backward. That is the point of the step pyramid in Figure 3.20: it looks like a staircase, but hikers can go up or down, laterally, or in more complex interactive dance patterns.

How do we know there are choice points in neuronal traffic flow? The anatomical connections indicate as much, but the fact that humans and animals constantly deal with *ambiguities* is an important source of evidence as well. Most words in natural language have more than one meaning (a fact we rarely notice consciously, but a glance at a good dictionary will show it). Dictionaries understate the degree of ambiguity in language because they are used by skilled native speakers who bring a great deal of contextual knowledge to their reading of verbal definitions. There is much that a dictionary writer can simply take for granted – but the nervous system cannot.

In the visual world we also encounter constant ambiguities that we do not bother to make conscious. Daylight changes color at sunset. When we walk through woods the light is filtered through green leaves. Wearing sunglasses filters colors, and even glass windows create reflectance patterns that change the visual world. Those differences rarely become conscious, because the visual system tends to maintain color constancy, sometimes from memory. But in the brain, those differences must be processed, and separated from color signals that we need to notice. Animals cannot afford to miss a predator stalking through the tall grass just because it's sunset, or because there are shadows from surrounding trees, or because there is an early morning mist. We need excellent visual brains to survive.

The famous Necker cube is shown in Figure 3.25(b). Figure 3.25(a) shows the two 'kissing faces' of the well-known face-vase illusion.

One might object that the visual ambiguities in the figures are so artificial that they would never occur in the natural world, but that would not be accurate (Figure 3.26). In any room with rectangular walls, the corners make up parts of a Necker cube. (To demonstrate this, just roll up a piece of paper into a tube, and look at the corners of a room. You should be able to flip it visually from an inside corner to an outside one.)

A cat stalking prey may look around a tree with only one eye, while the other eye just receives input from the tree: that leads to binocular rivalry, competition between the input to the two eyes. An animal walking through tall grass constantly receives different input to the two eyes, and some animals, like rabbits and deer, do not have overlapping visual fields at all, so that fused visual input is quite rare.

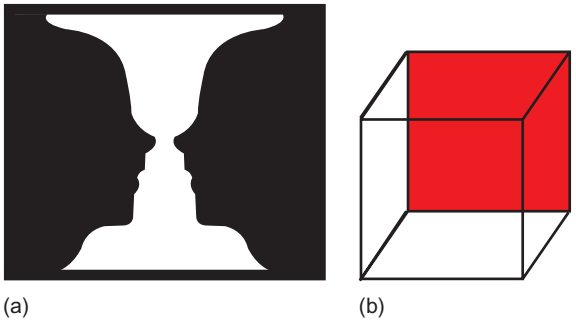

FIGURE 3.25 Ambiguous stimuli pose choices for interpretation. Two famous ambiguous figures: (a) the 'face-vase illusion' and (b) the Necker cube. The corners of a rectangular room will flip back and forth if they are seen through a tube that blocks out the visual surroundings. *Source*: Kim and Blake, 2005.

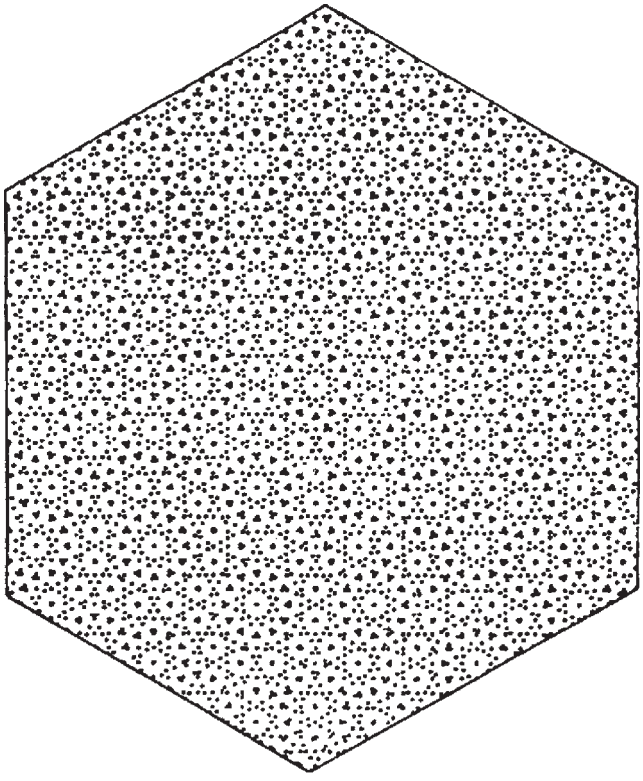

FIGURE 3.26 An ambiguous object: What is it? Shapes are sometimes hard to identify, even under natural conditions, as you can tell by trying to see objects in a bush or wooded area, watching birds during a morning mist, or looking at oncoming cars when the sun is in your eyes. *Source*: Feldman, 2003.

FIGURE 3.27 Which way is Humphrey Bogart looking? Human faces are among the most important objects in our environment. Being able to tell gaze direction and facial expression is a basic social skill. *Source*: Wexler, 2001.

Faces are biologically important for humans and other primates. Mother-infant bonding occurs face to face in our species, for example, as do competitive confrontations, mating interactions, and the like. But faces also show ambiguities. Which way is Humphrey Bogart facing in the white-on-black photo (Figure 3.27)? What emotion does his face express? Which picture looks more skeptical or suspicious?

3.6 Top-down or expectation-driven processing

The brain constantly generates expectations about the world it encounters. Walking downstairs in the dark, we have expectations about every step we take. In dealing with ambiguities like the figures shown here, we constantly make predictions about which of two perceptual interpretations is the best one. Most words in English are ambiguous, so that even as you are reading this sentence you are resolving ambiguities. The brain is driven by more than just input; it has many ways of biasing choice-points by means of *predictions* and *expectations*. *Lateral* processing is also important, as we have seen, to sharpen differences between neighboring stimuli in the visual array. As we will see later, selective attention allows us dynamically to adjust our sensory biases (see Chapter 8), and long-term memory strengthens synapses that are associated with accurate perception.

Maps and layers are not the only functional units. Many cortical regions are massively interconnected with each other, so that activity in one part of the cortex quickly spreads to other regions. A number of scientists believe, therefore, that the entire cortex, together with satellite regions like the thalamus, should be considered as a functional unit. This is often called the thalamo-cortical system. But to understand how those massive systems work, we will study their smaller components in some detail.

FRONTIERS OF COGNITIVE NEUROSCIENCE

The plastic brain

FIGURE 3.28 Paul Fletcher, PhD, Behavioral and Clinical Neuroscience Institute, University of Cambridge, UK.

For years, studies of learning in animals and humans have accounted for a large portion of experimental psychology research. It's easy to see why: A striking feature of animal behavior is the capacity to adapt – to learn which places and actions will bring pleasure, which will bring pain, and which are unreliable predictors of either. Added to this, the environment can be variable across time. A place or an action that was previously a reliable source of reward may rapidly become barren and the animal must be able to adapt to this, no matter how consistently rewarding that location previously has been. A key feature of the brain is its adaptability.

But how are we to understand this adaptability in terms of the brain changes that must underpin it? The insights derived from neuropsychology alone, from the accidental occurrences that form the basis of lesion work, are not optimal because the processes that we are attempting to scrutinize are dynamic and may well involve plasticity that is distributed across the brain rather than localized to a single region. In this regard, we can see the

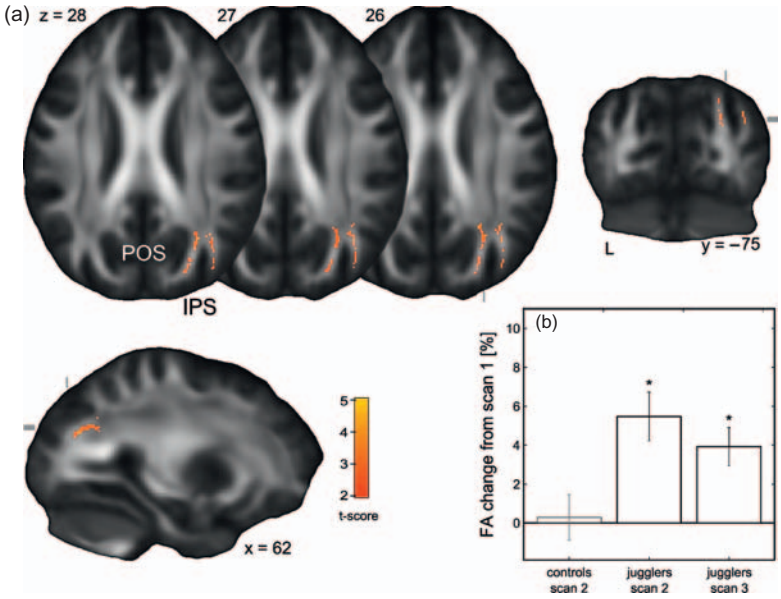

FIGURE 3.29 White matter changes occurring as a consequence of juggling training. (a) Colored voxels represent clusters (corrected $p < 0.05$) of significant FA increase from early to late training, superimposed on the mean FA map. (b) Mean FA change from scan 1 from within the cluster shown in (a). Error bars represent standard errors. (*significant relative to baseline at $p < 0.05$; IPS = intraparietal sulcus, POS = parieto-occipital sulcus.) *Source*: Scholz *et al.*, 2009.

potential value of the remarkable developments in neuroimaging that have occurred over the last two decades. Although much neuroimaging has been region-orientated, emphasizing functional segregation rather than functional integration, latterly there have been concerted attempts to understand learning, and the theoretical models that describe learning, in terms of systemwide changes in brain structure and function.

From a functional perspective, the brain is indubitably an ever-changing machine with regional activity modulated by experience. However, the change in localized regional activity is only a small part of the story and more recent approaches to functional neuroimaging have developed ways of exploring interregional relationships, characterizing the learning process in terms of strengthening or weakening influences that different regions may exert over each other. A recent study has shown that the human brain is exquisitely sensitive to incidental contingency relationships between auditory and visual stimuli (den Ouden *et al.*, 2009). Intriguingly, though experimental participants in this study were largely unaware of these contingency relationships, there was a measurable increase in the degree of connectivity between primary auditory and visual areas as a consequence of experiencing them, even though they had no bearing on the task that was being performed. Could such observations help to explain how extraordinarily able people are to function, under certain circumstances, as "intuitive statisticians" (see Shanks, 1995)?

These functional connectivity measures are fascinating but their structural underpinnings have been elusive. However, further recent developments in MRI have begun to allow us to determine how the key components of structural connectivity – the white matter tracts – may also change as a consequence of experience. Scholz and colleagues (2009) showed that learning to juggle was associated with changes in both gray matter density and in the white matter tracts (Figure 3.29). That is, as a consequence of simple practice in a motor skill, the brain is changing its structure in terms of gray matter density and its connectivity, in terms of white matter tracts. This is groundbreaking work; for many years there have been assumptions that the brain is structurally immutable. Insights such as this point to both a functionally and structurally evolving organ, surely a step forward in refining our understanding of learning processes.

Observations such as these at the macroanatomical level must surely complement more detailed observations of synaptic change at the microanatomical level, and will provide the basis for a more complete understanding of the brain's adaptability to changing contingencies in the environment. This understanding itself will be an absolute prerequisite for developing our understanding of the aberrant learning and connections that might characterize certain mental illnesses, most notably schizophrenia (Fletcher & Frith, 2009).

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4.0 HOW NEURAL ARRAYS ADAPT AND LEARN

Learning has been studied very intensively in layered arrays of simulated neurons. After a slow start, the study of 'neural nets' took off in the 1980s (Rumelhart and McClelland, 1986a, b). *Connectionism* has been the theoretical framework for much of this movement. Much of this chapter reflects lessons learned from the connectionist movement (see also Neural Darwinism, below). While neural nets were first explored in the 1950s, the early efforts encountered difficulties in doing useful processing. By the 1980s, it became clear that adding an additional (hidden) layer would solve many of those problems, and that feedback also helped. These insights helped to launch the connectionist movement.

4.1 Hebbian learning: 'Neurons that fire together, wire together'

Donald Hebb (Figure 3.30) proposed, in 1949, that assemblies of spiking cells could learn an input pattern by strengthening the connections between cells that fire at the same time. This idea is encoded in the slogan that 'neurons that fire together, wire together'. It is a very useful learning method for neural networks, and there is some direct evidence for *Hebbian learning* in the nervous system.

The key idea in Hebbian learning is that more efficient synaptic connections are the physical substrate of learning and memory. As Figure 3.31 points out, however, there are a number of ways in which synaptic transmission could become more efficient. Two neighboring neurons can gain more synapses, the synapses may be supplied with more nutrients that lead to more neuro-transmitter chemicals, the receptors for those neuro-transmitters could become more efficient, and so on.

Two kinds of synaptic changes are believed to be involved in learning; they can be considered strengthened excitation and strengthened inhibition. Long-term increases in excitation from one neuron to another are called *long-term potentiation* (LTP). Long-term decreases are called *long-term depression* (LTD). There is some evidence for both in the hippocampus.

It is always important to remember how long the brain took to develop – the mammalian brain is some 200 million years old and, prior to that time, even earlier vertebrate brains were able to develop high degrees of sophistication for their ecological niches. For that reason, while there is solid evidence for learning mechanisms like Hebbian learning, it is believed that there may be other mechanisms as well.

FIGURE 3.30 Donald R. Hebb: cell assemblies that learn. Donald R. Hebb was one of the most influential theorists for cognitive science and neuroscience. He clarified the notion of a 'cell assembly', and proposed the best-known learning rule for neural networks, summarized by the slogan 'neurons that fire together, wire together'. *Source*: Brown and Milner, 2003.

Hebbian learning can be shown visually as a thickening of lines between the nodes of a network, like the simple cell assemblies of Figure 3.32. In this case, a visual circle is activating corresponding cells in a model of early visual cortex. The nodes in this circle represent points or small regions in the visual field, and they are being strengthened by correlated firing. That is the theory. Figure 3.33 shows a remarkable set of findings that seems to confirm the model, with actual strengthening of connection probabilities ('weights') in the hippocampus of the cat. The brain is a large place, of course, so that finding apparent Hebbian learning in one location does not prove its existence everywhere. Nevertheless, this is an encouraging result, and suggests that the overall direction is productive.

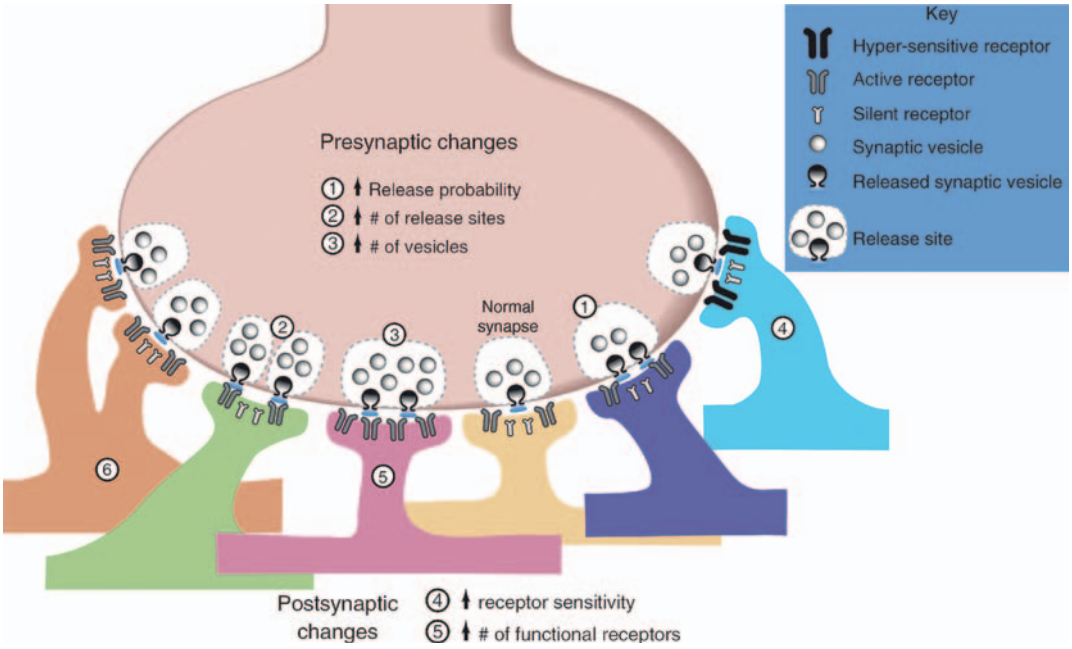

FIGURE 3.31 Hebbian synapses and long-term potentiation. There may be several ways to increase the efficiency of synaptic connections. *Source*: Byrne in Squire *et al*., 2003.

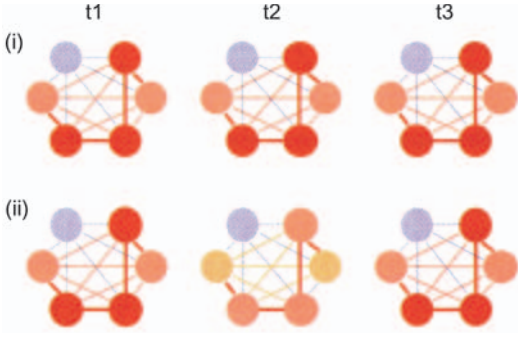

FIGURE 3.32 Hebbian learning in cell assemblies. Neurons are represented by circles and their connections by lines. Redder colors represent more active units and thicker lines indicate stronger connection weights between units. At time t1, the cell assembly encodes input in its connection weights. In this example, memory is retained at times t2 and t3. More realistic models may show forgetting over time, and permanent memories may need to be strengthened by repeated exposures to the same stimulus. *Source*: Abraham and Robins, 2005.

In Figure 3.34 a simple network may be used for classifying input patterns. In this case, there are two-way connections vertically, with lateral inhibition in each layer of the network. This is sometimes called a 'local' network, because it does not involve learned strengthening of connection weights. It is nevertheless useful for explaining some basic cognitive phenomena (Rumelhart and McClelland, 1986b).

Figure 3.35 shows a breakthrough in network modeling. Early models were devised in the 1950s by Rosenblatt (1962) and others. These were one or two-layer models, and were found to have logical limits when it came to basic brain functions like learning and recognizing patterns. For some time neural models went into decline, until some twenty years later, when it was realized that adding a layer of 'hidden units' and allowing the network to adjust its connection weights could solve the earlier difficulties. Figure 3.35 shows a classical three-layer feedforward network with a hidden layer and adjustable weights. This network can learn efficiently when its output is compared to a wanted output pattern, and the network weights are systematically adjusted to come closer and closer to the set goal. This process is called 'back-propagation', and is much like a negative feedback loop, the kind that we find in thermostats. This kind of network is used most often today, though mathematical and empirical studies continue to advance the understanding of brain-like information processing.

Figure 3.36 shows a self-organizing auto-association net, in which the output is led to match the input. That is a useful strategy for recognizing patterns like the sound of a familiar voice. Self-organizing systems

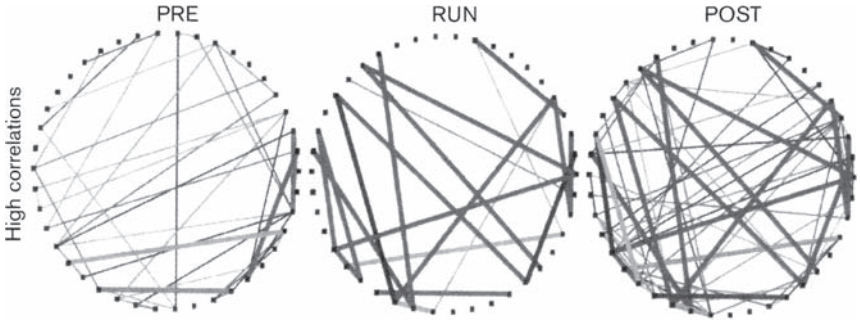

FIGURE 3.33 Observed Hebbian learning. Strengthening of neuronal connections has been observed directly in hippocampal neurons in the cat. *Source*: Sutherland and McNaughton, 2000.

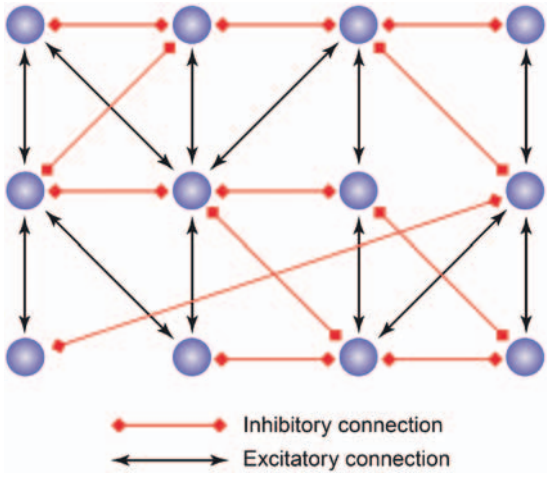

FIGURE 3.34 A simple network. Notice the combination of excitatory and inhibitory connections. *Source*: Palmer-Brown *et al.*, 2002.

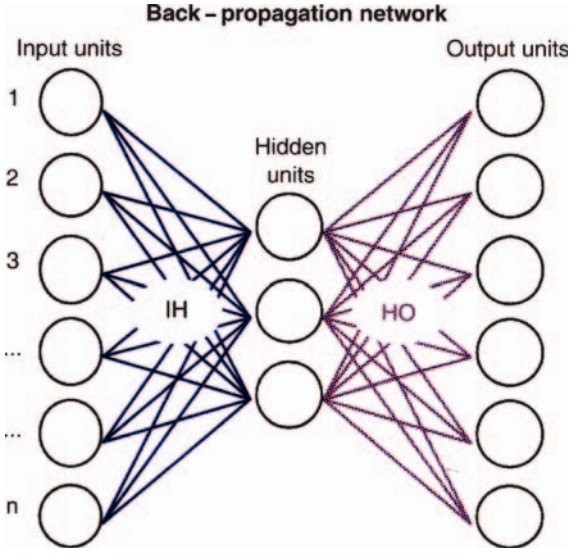

FIGURE 3.35 A classical three-layer network. The hidden layer makes the network much more flexible. Back-propagation allows network output to be compared to a teaching source, and changes network weights to match the source. Thus, the network can learn from feedback to approach its goal. *Source*: Abraham and Robins, 2005.

arise in nature in many situations. Biological organisms can be viewed as self-organizing systems, and perhaps nervous systems are a refinement based on biological cells. However, a marker of human culture is the immense amount of teaching that takes place. From birth onward, we learn from other people. Thus, culture may go a few steps beyond self-organizing learning systems, and develop knowledge and skills that can be taught, more like the network shown in Figures 3.35 and 3.36.

Figure 3.37 shows how a self-organizing network may be applied to the fundamental human problem of face recognition. Babies learn to respond to normal faces (but not scrambled faces) early in their lives, and soon can tell familiar from unfamiliar ones. This example is much simpler than the task that babies solve so effortlessly, because it involves only a line drawing. The network learns to predict a mouth at the bottom of the picture, and two eyes on top. But it could not function under more subtle three-dimensional visual conditions, in changing light conditions, moving mouths, eyes and heads, and so on. Nevertheless, the face recognition network in Figure 3.37 gives us a way to try to understand how the brain performs a basic life task (see Chapter 6).

4.2 Neural Darwinism: survival of the fittest cells and synapses

The neuroscientist Gerald Edelman has proposed that the brain is a massive *selectionist* organ. Edelman's

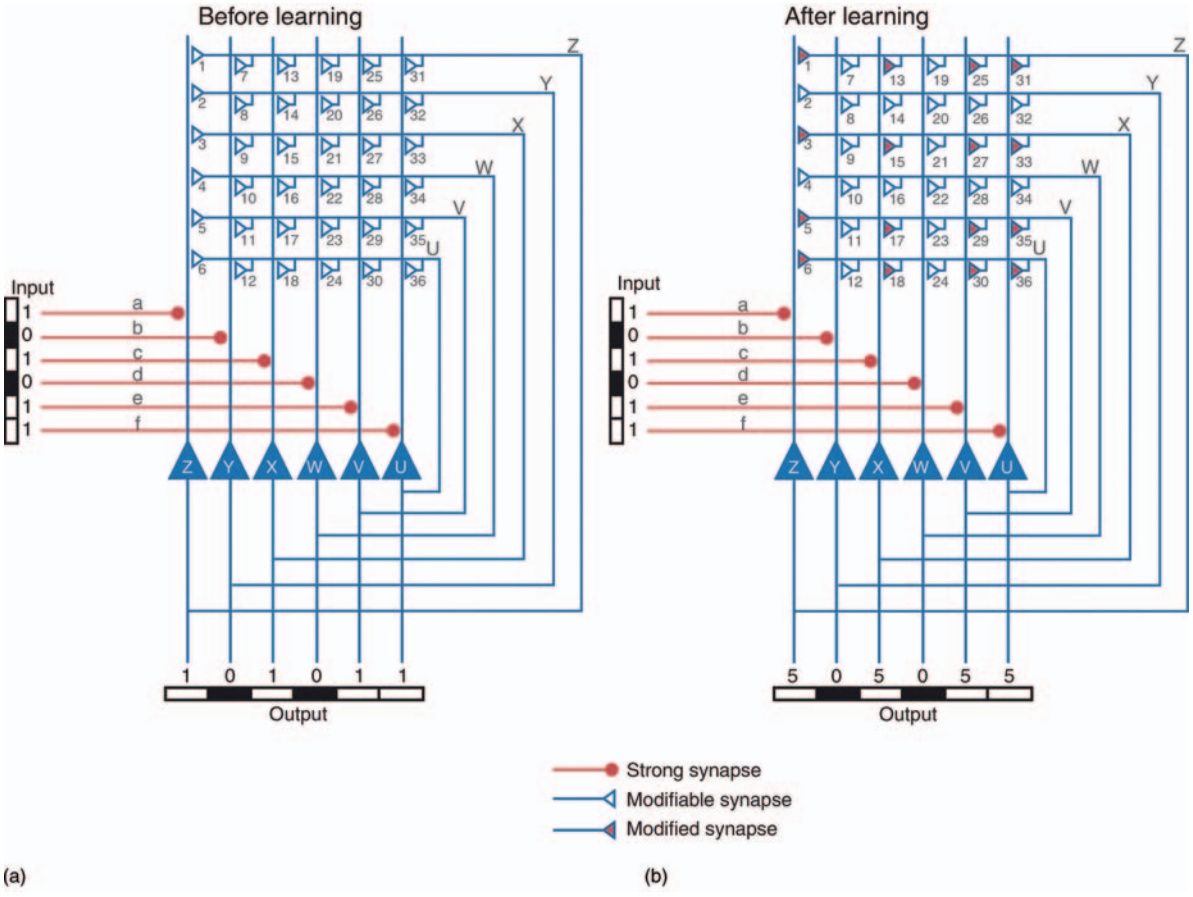

FIGURE 3.36 A pattern recognition net. An auto-associative network matches its output with its input, a feature that is useful for recognizing patterns, like faces or cars. On the right side some of the neurons have turned red, to show that their connection strengths have changed after learning. *Source*: Byrne in Squire *et al.*, 2003.

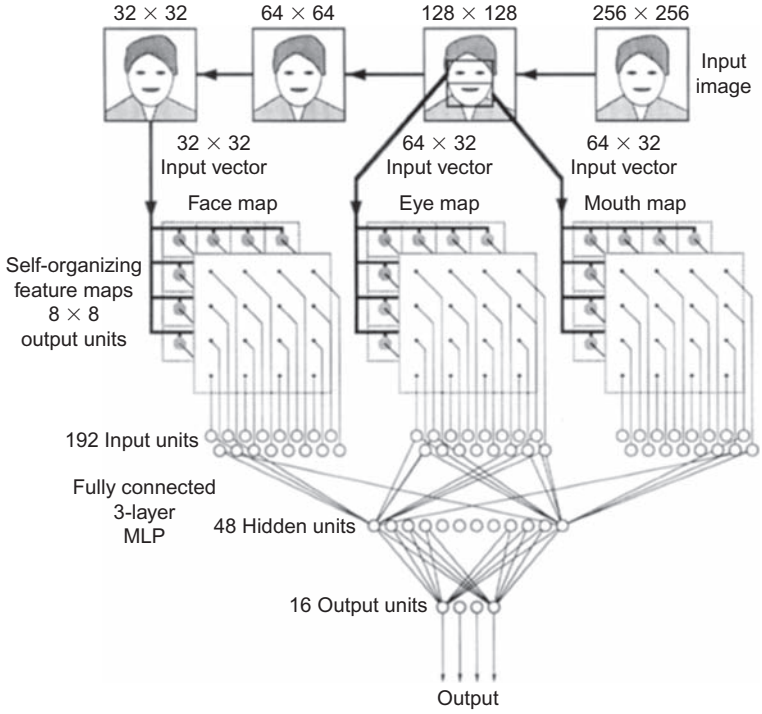

FIGURE 3.37 A face recognition network. Recognizing faces is a basic problem for the visual system. With simple line drawings face-recognition can be done. But when real faces are seen under natural lighting conditions the job becomes far more complex and variable. Notice that is a three-layered network. *Source*: Luckman *et al.*, 1995.

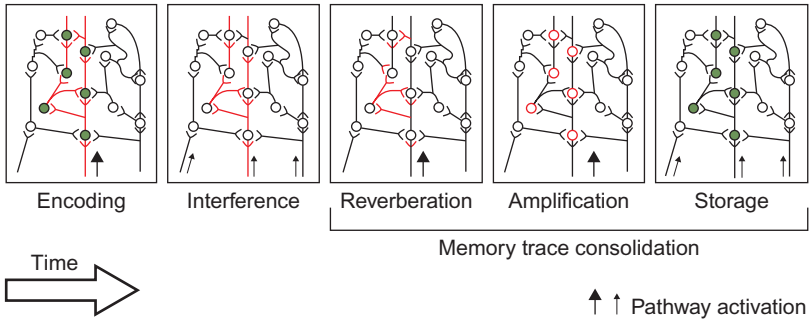

FIGURE 3.38 An example of Neural Darwinism in learning. This figure shows stages of encoding a neural activation pattern until dynamic synaptic activity allows permanent connections to be strengthened, thereby enabling memories to be stored in the same locations where the original connections were made. *Source*: Ribeiro *et al.*, 2006.

theory is called *Neural Darwinism*, since it suggests that neurons develop and make connections following Darwinian principles. In biological evolution, species adapt by *reproduction*, by *mutations* leading to diverse forms, and *selection* among the resulting repertoire of slightly different organisms. Over long stretches of time this weeding process yields species that are very well adapted to their niches. A similar process occurs in the immune system, where millions of immune cells adapt to invading toxins. Cells that can successfully match the invaders multiply, while unsuccessful ones dwindle in number. The immune system can therefore learn to recognize and combat even novel invaders from the environment. *Selectionism* therefore leads to very flexible adaptation.

According to Edelman (1989), the brain has two stages of selectionist adaptation. The first begins soon after conception, when the first neurons are born, multiply, differentiate, and are selected if they fit their local niches. The outcome of this stage is a collection of neurons that looks like a brain. The second, overlapping stage, begins when neuronal connections are made. Adaptive connections tend to survive while others die out. A kind of Darwinian selection therefore operates both developmentally and as a result of learning (Figure 3.38). Two-way connections between neuronal maps allow for re-entrant (two-directional) processing. If a re-entrant process is stable, it will tend to survive among all the other transitory waves of activation in the brain. If not, it will simply fade away.

If we add the Hebbian principle that 'neurons that fire together, wire together', a stable cell assembly will tend to make stronger connections between its units. Thus, the Darwinian process would lead to longer-lasting neuronal 'species', cell assemblies that enable the tasks of adaptation, learning, pattern recognition, and the like.

These ideas have been refined by brain studies and computer simulations. The Darwin series of robots has employed selectionist principles to simulate how regions like the hippocampus seem to work. In Figure 3.39a, a neural Darwinist 'rat' simulates the behavior of a rat in a Morris water maze, in which the animal needs to find a platform hidden under the surface of the water, which allows it to rest. In Figure 3.39b, a selectionist robot is learning to play soccer. While these tasks are very different, they are learned using the same principles.

4.3 Symbolic processing and neural nets

Standard computer programs use symbols. That is, they employ logical and mathematical expressions. Neural nets can be expressed in mathematical terms, but they tend to be more *parallel* (with many different computations happening at the same time), and *distributed* (able to process information in different places, using different memories, and so on). That is to say, neural nets are closer to biological information processing than to standard algebra and logic.

However, humans created mathematics and logic, and natural language makes us very good at understanding symbolic expressions. Most of the words we use are symbols referring to some class of events in the world. Furthermore, neural nets are easily translated into mathematical expressions.

How can these two different computational philosophies be reconciled? One method suggested by McClelland and Rogers (2003) is shown in Figure 3.40, where a neural network was designed to express symbols (like 'sunfish', and 'grow') and their logical

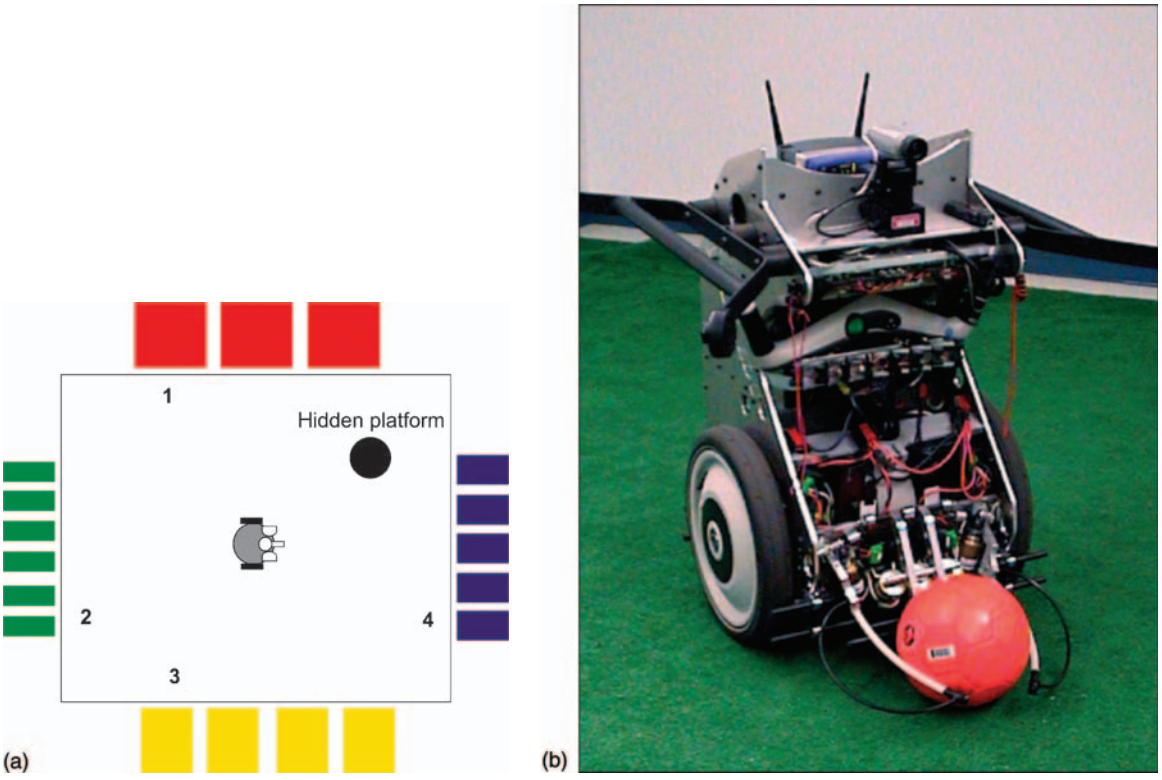

FIGURE 3.39 (a) This figure simulates a rat in a Morris water maze, swimming until it finds a platform to stand on. The brain-inspired simulation creates a neural map of the water maze, so that the simulation learns to find the platform. (b) A robot uses a Neural Darwinist brain model to learn to play soccer. *Source*: Neurosciences Institute, Krichmar, 2006, with permission.

relations (like 'has a property'). For a human mind, this is a complicated way of expressing a simple idea like 'sunfish can grow'. But for massive neural networks with many millions of units and trillions of connections – such as our brains – the McClelland and Rogers version is more compatible with the wiring of the brain.

In sum, it seems that neural nets can be translated into symbolic form, and symbols can be converted into neural nets. Thus, the debate over symbolic versus neural net expressions is not either-or. The scientific question therefore would seem to be which theoretical language is more useful for any given problem. If we want to understand brains at the level of neurons, networks are quite natural. If we want to understand the grammar of English, symbols might be better. It all depends on the question we want to explore.

Adaptation and *representation* are two complementary ways of thinking about the brain. We will see evidence that brains are specialized for knowing the world. There is also evidence that brains behave in adaptive ways, adjusting constantly to changing conditions. Both of these ideas seem to be fundamental. Some findings may seem more adaptational, others more representational. We will find both perspectives useful.

5.0 COORDINATING NEURAL NETS

The brain is often called a massively parallel organ, because neurons appear to be working quite independently of each other. There is no central command post that tells all neurons exactly what to do.

There are a number of ways in which neurons can be coordinated, however. One way is for large-scale rhythms to pace populations of neurons, much like the conductor of a symphony orchestra. When many neurons fire in unison, their activity adds up, just as a large crowd of people sounds louder when they are chanting in unison. There is a limit to this, however. Epileptic seizures have long been believed to be caused by neural scar tissue, called the epileptic focus,

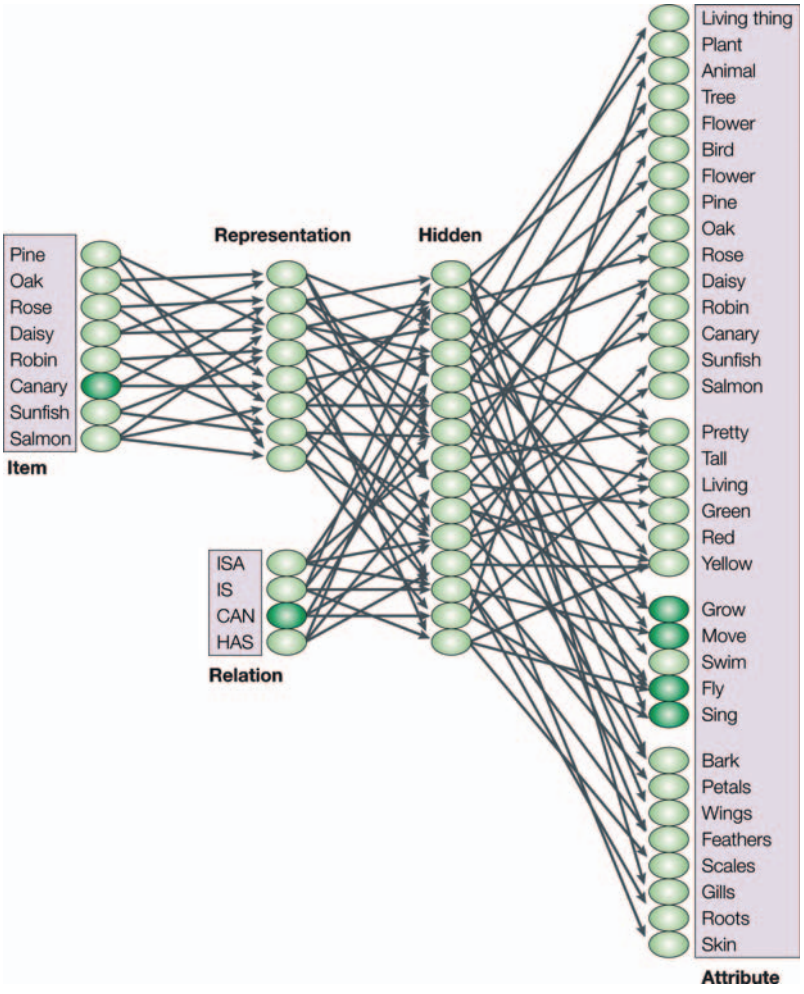

FIGURE 3.40 Neural nets can handle symbolic expressions. In this example, a network represents a large set of propositions such as 'a robin is a bird' and 'a rose has petals'. *Source*: McClelland and Rogers, 2003.

which sends out intense, slow, and regular waves that recruit other brain regions, so that spreading populations of neurons begin to chant the same song. The result is a loss of consciousness and physical seizure activity.

Obviously, the brain must balance the degree of pacing and coordination against the need for local neurons and their neighbors to work on local functions. There must be a balance between *integration* and *differentiation* (Edelman and Tononi, 2000).

Figure 3.41 shows averaged correlations between visual regions while the subject was watching a movie. As you can see, similar regions in both hemispheres, symbolized by (l) and (r), tend to become active at the same time, as indicated by the red and yellow lines. Since both sides receive basically the same input from the two eyes, this result makes good sense. In addition, within each hemisphere strong correlations show up between early visual analysis and the area for visual object perception (LO). However, because this study used functional magnetic resonance imaging (fMRI) and averaged over long periods of time, we are not seeing fast correlated activity. This is a limitation of the specific methodology, which scientists are currently working to overcome. A number of recent results show much faster gamma and theta correlation, for example, at the frequencies at which the brain seems to do much of its work (Fries, 2005).

Regular EEG rhythms are now believed to signal distinct, coordinated processes. For example, a high density of gamma rhythms has been related to conscious visual perception, and to the process of discovering a solution to a simple word problem. Alpha rhythms are traditionally associated with an absence

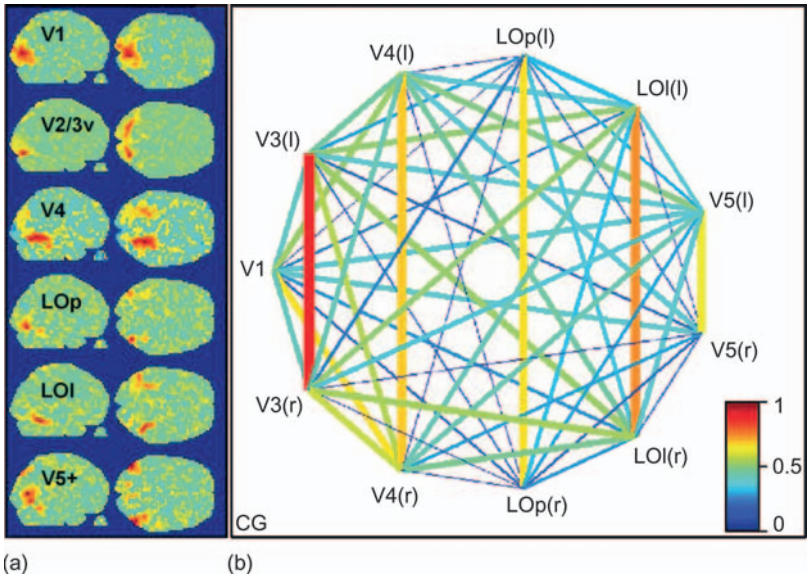

FIGURE 3.41 Correlated brain regions while watching a movie. A dramatic illustration of correlated activation in the visual cortex while the subject was watching a movie. The upper half of the large panel is in the left hemisphere, the lower half in the right hemisphere. V areas with the same number correspond to the left and right sides, which are usually connected across the midline. 'Hotter colors' and thicker lines indicate higher correlations between visual areas. Notice that the strongest correlations are between corresponding regions of left and right hemispheres. Lop = posterior part of the lateral occipital complex; LOI = lateral part of the lateral occipital complex; (l) = left hemisphere; (r) = right hemisphere. On the left are local fMRI activations. *Source*: Bartels and Zeki, 2005.

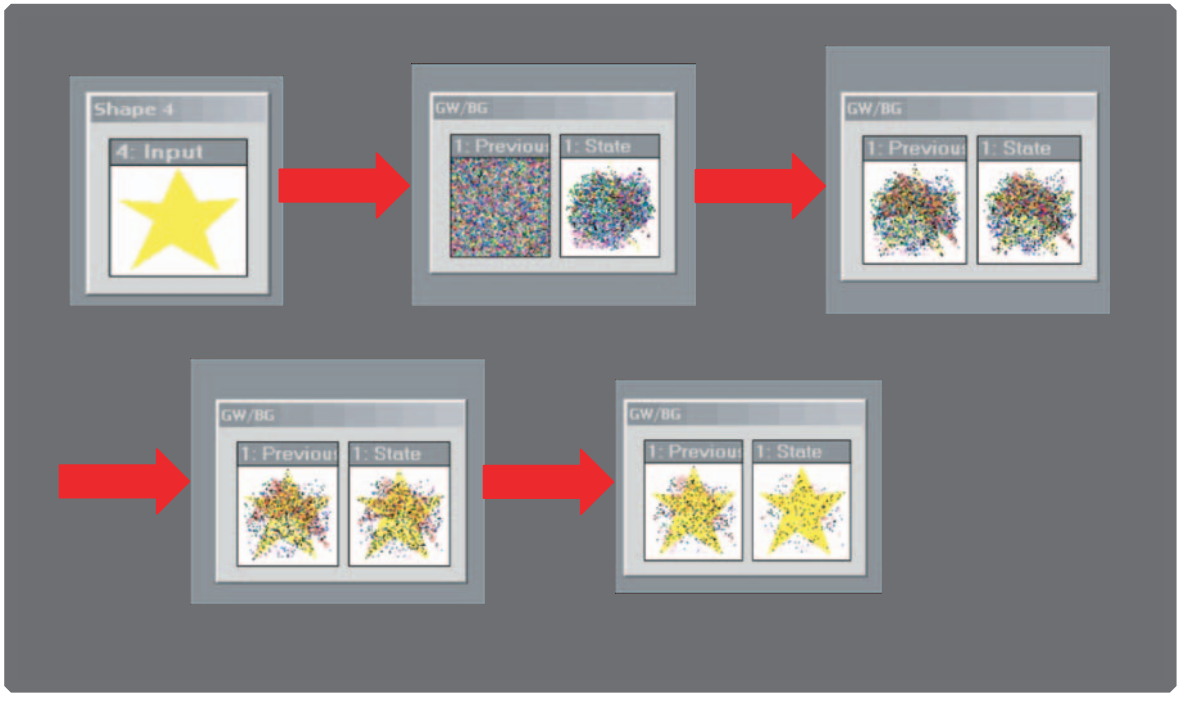

FIGURE 3.42 A pattern-recognition network. The yellow star in the upper left panel provides an input shape into a pre-trained neural network. Later panels give the current state of the network, shown in an array of colored dots. Notice that the yellow star emerges slowly, as the network recognizes the input, and eliminates alternative possibilities. *Source*: M. Shanahan, Imperial College London, with kind permission.

of focused attentional tasks, but theta rhythms are now believed to coordinate the hippocampal region and the frontal cortex during the retrieval of memories. And delta rhythms, the traditional signal of deep sleep, are believed to group fast neuronal activity in order to facilitate the consolidation of learned events (Kemp *et al*., 2004).

Figure 3.42 shows a very simple and reasonable hypothesis about how regular brain rhythms may coordinate the firing of millions of separate cells. Neurons that fire at the peak of the alpha wave (for example) add a tiny amount of electrochemical activity to the whole chorus. Neurons that fire during the trough of the regular rhythm subtract their activity. Thus, neurons that fire in sync with the dominant rhythm are strengthened by feedback from the millions of other neurons that are keeping up the alpha rhythm, while those that are out of sync are weakened. Such a mechanism would tend to reinforce rhythmic firing.

As we have already pointed out, however, simple synchronized firing is not enough. Different coalitions of firing neurons must be able to generate different input representations, which can compete against other coalitions to recruit new members. Such a model is shown in Figure 3.38, where it supports a kind of Neural Darwinian competition between different populations of nerve cells.

5.1 Functional redundancy

When engineers build airplanes, they always introduce *functional redundancy* into their designs, so that there is a backup for critical functions that could go wrong. If one jet engine fails, most aircraft are designed to fly using the remaining ones. Humans and animals also evolved with functional redundancy in all their organ systems – we have two lungs, two sides of the heart, and so on. The brain is no exception. Even the loss of the speaking half of cortex can be overcome, if it occurs early in childhood. The brain can often keep working, even in the face of some damage.

6.0 SUMMARY

The most basic question in cognitive neuroscience is how nerve cells can combine to perform complex cognitive functions, like perception, memory, and action. That problem has not been solved in all its richness, but significant progress has been made. The integrate-and-fire neuron has been well studied, and is understood in considerable detail. However, there are a great many kinds of neurons, types of transmission between them, and neurochemicals that play crucial roles. We take the integrate-and-fire neuron to be our prototype, because it is well established and can be simplified, so that its action can be understood by detailed modeling. Both artificial neural networks (ANN) and biologically inspired networks are useful for this purpose.

Neurons sometimes make up simple circuits, like the knee-jerk reflex. More often, however, they organize themselves into large two-dimensional arrays, which link higher and lower level arrays into hierarchies. All the sensory and motor systems can be viewed as such complex hierarchies. In vision, touch, and motor control, arrays of neurons are topographically arranged as 'maps' of the spatial surroundings. The visual system, for example, can be viewed as a hierarchy of topographical maps.

Hierarchies are not rigid, one-way pathways. They allow signals to flow upward, downward, and laterally. A major function of downward flow of information in the sensory systems is the need to resolve ambiguities in the input. Ambiguities are common in visual scenes, but also in language and the other senses. In motor systems, upward (bottom-up) flow of information is similarly useful to help make choices in output plans and motor commands.

Lateral inhibition is a widely used biological strategy for emphasizing differences between inputs, like two patches of light and dark in a visual scene. Cells in the sensory systems have receptive fields that are attuned to specific types of input, such as line orientation, color, movement, shape, and object identity. As the visual maps go deeper into cortex, their spatial resolution becomes less, but their ability to integrate large amounts of information goes up. While we study the sensory and motor systems separately, the brain is a giant sensorimotor engine, which allows constant interaction of input and output at all higher levels.

Spatial arrays of neurons support spatial coding of information, but there is temporal coding as well. The major regular rhythms of EEG are believed to correspond to massive coordinated activities among large populations of neurons. Recent research suggests that gamma activity may be involved in such processes as sensory integration into conscious percepts, and theta has been associated with retrieval from long-term memory.

7.0 STUDY QUESTIONS AND DRAWING EXERCISES

7.1 Study questions

1 Describe the basic function of an integrate-and-fire neuron.
2 What is lateral inhibition and how does it relate to perception?
3 Explain how sensory and motor regions can be viewed as hierarchies.
4 Describe the role that re-entrant (two-way) connections play in brain function.
5 What is Neural Darwinism and what aspects of brain processes does it relate to?
6 List three or more common features of sensory systems.

7.2 Drawing exercises

1 Label the parts in Figure 3.43.
2 Draw Hebbian learning of cell assemblies for a visual circle. What slogan describes Hebbian learning?

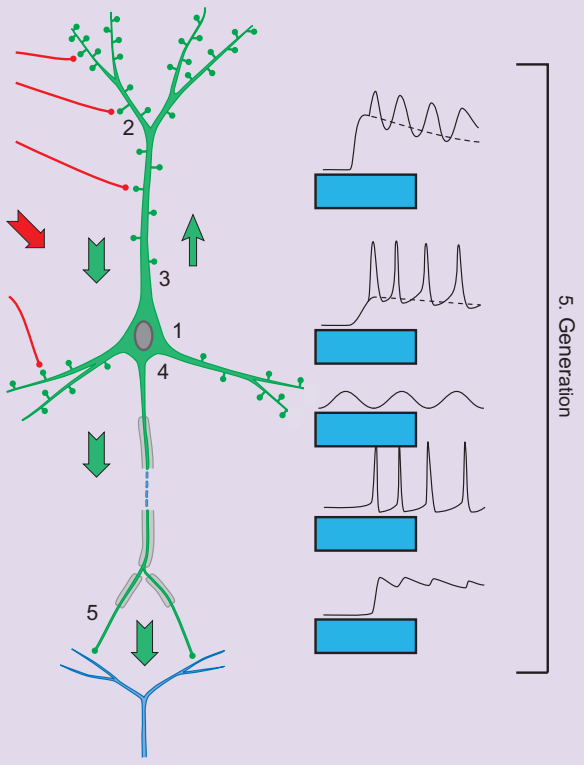

FIGURE 3.43 An idealized neuron. A simplified neuron for you to label.

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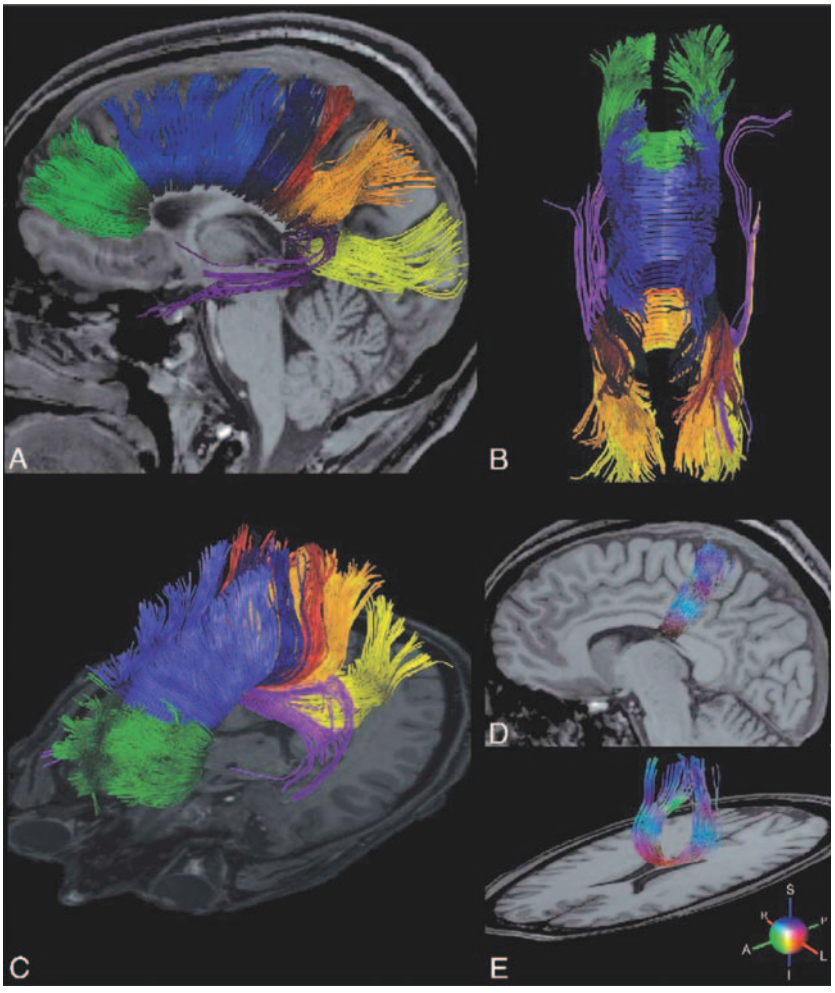
I believe that the study of neuroimaging has supported localization of mental operations within the human brain.

Michael I. Posner (2003)



Different views of the 'internal highway system' of the cortex – fiber tracts running through the inner brain, using a method called Diffusion Tractography. All fibers in these images are running crosswise across the corpus callosum, and then arch upward like fountains on either side. (A) is a side view, showing fibers sweeping upward in the left side of the hemisphere. Green fibers are in front (prefrontal), light blue begin and end in premotor cortex, dark blue fibers are coming from the motor cortex itself, orange ones are parietal, and yellow fibers flow from the occipital cortex on one side of the brain to the other. The violet fibers along the side run between the temporal lobes on each side of the brain. (B) shows just the fiber bundles alone, on both sides of the brain, viewed from back (yellow) to front (green). On the bottom right, note the orientation compass: A, anterior; I, inferior; L, left; P, posterior; R, right; S, superior. *Source:* Hofer and Frahm, 2006.

CHAPTER

4

The tools: Imaging the living brain

OUTLINE

1.0 INTRODUCTION

This chapter presents the tools of brain recording from the viewpoint of an intelligent user, trying to understand how the brain works. The Appendix presents the tools in more detail.

A perfect observer of the mind-brain would be able to follow tens of billions of neurons and sample each one a thousand times per second. The perfect observer should then be able to track the constantly shifting interplay between smaller and larger groups of neurons, making trillions of possible connections. By analogy, a perfect spy satellite in space would be able to see every single human being, as well as the changing relationships between individuals and groups, from families to whole nations.

Such a perfect observer does not exist. Our understanding of the brain is a kind of collage of many fragments of the puzzle, glued together to make a reasonable picture of the whole. But thinking about a perfect observer gives us the parameters we can aim for.

Brain imaging has been a breakthrough technology for cognitive neuroscience, building on decades of cognitive psychology, behavioral conditioning, psychophysics and brain science. Before imaging techniques matured, our knowledge came from animal studies and the haphazard injuries incurred by human beings. But brain injuries are extremely imprecise, and even to locate the

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

damage, neurologists often had to rely on post-mortem examination of the patients' brains – as in the case of Broca's and Wernicke's patients discussed in Chapter 1. The brain can often compensate for damage, so that lesions change over time, as cells die and adaptation occurs. Therefore, post-mortem examinations do not necessarily reflect the injury at the time of diagnosis. Animal studies depend on presumed homologies – similarities across species – that were often not convincing to everybody. No other animals have language, and other distinctively human specializations. It was therefore very difficult to understand how brain functions in animals mapped onto human cognition.

Many of these problems were resolved when it became possible to observe the living brain, first by electroencephalography (EEG), then by X-rays, then computer *tomography* (CT, the study of slices – from the Greek word for 'slice', *tomos*) based on X-rays, positron emission tomography (PET) and magnetic resonance imaging (MRI, etc.). Today, we have perhaps a dozen techniques that are rapidly becoming more precise. Medical needs often drive this very expensive technology because it applies to many organs in the body. As a result, we now have ways to study the distribution of billions of neurochemical receptors in the brain, the thickness of cortex, the great highway system of white fiber bundles, and most important for cognitive neuroscience, the *functional* activity of the brain – the basis of its adaptive capacities. New advances are allowing scientists to investigate not only functional activity located in specific brain regions, but also to measure the dynamic pattern of connectivity between them. Some of the massive 'wiring' of the brain is shown in the figure at the beginning of the chapter, but like the world wide web, the wiring is only part of the story: there are ever-changing dynamic connections made between neural populations that can alter in a fraction of a second.

1.1 Brain recording: more and less direct measurements

Some neuroimaging methods pick up neuronal activity more directly than others. If we place an electrode next to (or inside) a neuron we can record its electrical activity, typically its axonal spikes. This single-electrode measurement can be seen as a direct measure of the electrical activity of the neuron. As we have seen in Chapter 3, however, neurons do more than fire spikes. The input branches of a neuron, the dendrites, also engage in important activity. By recording different parts of a neuron we get somewhat different measures of its activities.

This is nicely illustrated in a recent study by Quiroga and colleagues at Caltech (Quiroga *et al.*, 2005) (Figure 4.1). These researchers found that a single neuron in the medial temporal cortex was selectively activated by pictures of actress Jennifer Aniston. It was not activated by pictures of other actresses, or actors, or by other kinds of images such as houses, scenery, and objects. The researchers also found other cells that were highly selectively activated, including a neuron that was sensitive to pictures of actress Halle Berry and one for the Sydney Opera House. It is important to keep in mind, of course, that we are sampling just some out of billions of neurons. In all probability, there is a complex network of related neurons, and a lucky hit will reveal a Jennifer Aniston or Sydney Opera House fan.

The researchers used the axonal firing rate of single neurons as the measure of their activity. Would this mean that this single neuron 'knows' about Jennifer Aniston? Not at all. We should rather think of the activity of this cell as a representative for a large and widely distributed network of neurons that are sensitive to one particular face. If this neuron were lost, the person would still be able to recognize Jennifer Aniston. The brain as a whole would not show a detectable change.

Single cell recordings are only rarely possible in human subjects. It is ethically allowable in patients with medically untreatable epilepsy or brain tumor, where the only treatment is surgical removal of the affected region. Depth electrodes are inserted to identify vital cognitive areas such as the language areas. If such a surgical procedure is required, scientists may be allowed a brief time to test a subject while the electrodes are in place.

1.2 The time-space tradeoff

Today's most popular methods are shown in Figure 4.2. Notice that they do not yet have the space or time resolution needed to track single neurons, or even small clusters of neurons, like the columns of the cortex. They are gaining ground, however. Techniques like fMRI, which record physiological changes like blood oxygenation, are typically thought to have good spatial resolution and relatively poor temporal resolution. fMRI has a response time of about six seconds, because changes in local blood supply take some time – too slow for tracking neurons and neuron populations

FIGURE 4.1 The Jennifer Aniston neuron. Quiroga and colleagues (2005) found a neuron in the left hippocampus that selectively responded to different views of the actress Jennifer Aniston. (a) Responses in 30 of a total of 87 images are shown. (b) Axonal spikes to 30 out of 87 photos are shown. Numbers indicate the image number; graph indicates number of neural spikes recorded. Single neurons are likely to represent large networks with different sensitivities and preferences.

directly. However, some recent studies show fMRI signal reflects neuronal firing six seconds before.

fMRI has very good spatial specificity compared to EEG and magnetoencephalography (MEG), which use electrical and magnetic signals respectively. Thus, fMRI is often used to localize brain functions. But EEG and MEG have excellent temporal resolution – almost instantaneous – and relatively poor spatial precision. They can track cell populations firing and fading over tens and hundreds of milliseconds, but it is hard to know *which* set of neurons is causing the signal. Some studies therefore combine EEG with fMRI to obtain the best temporal *and* spatial precision. A great deal has been learned with combined recording techniques.

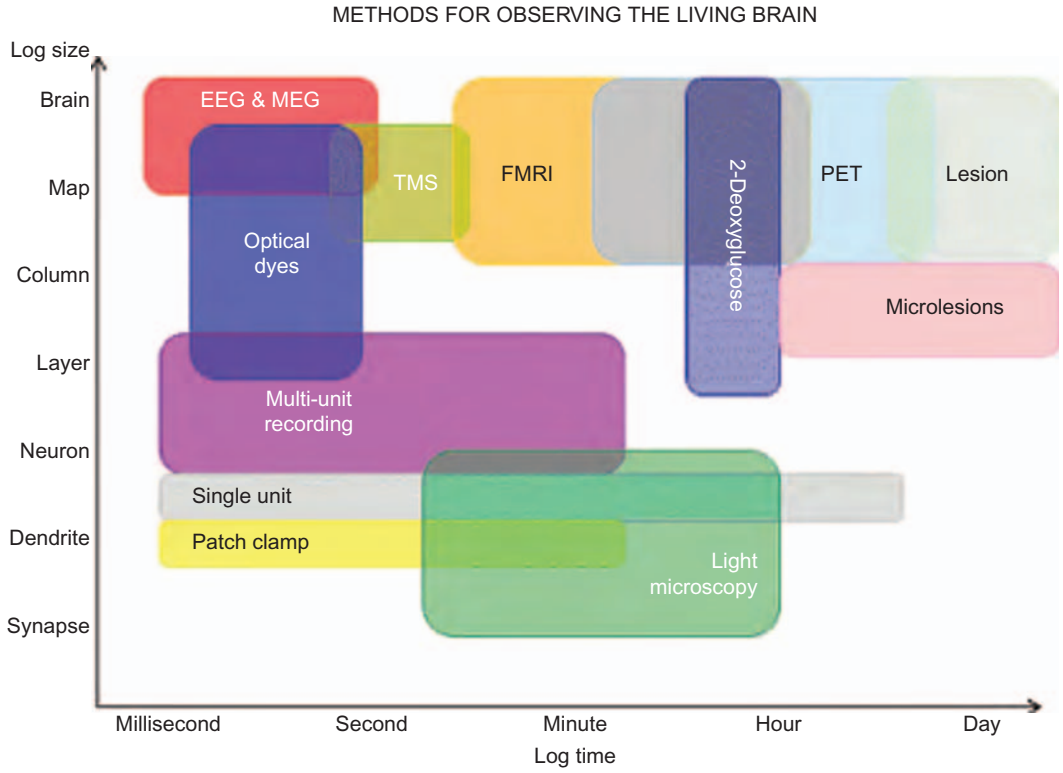


FIGURE 4.2 Pros and cons of imaging techniques. Different imaging modalities have different resolution. While some approaches have a very high temporal resolution but a low spatial resolution, other modalities have an opposite relation.

Here we present some MRI images to demonstrate the ability they provide to map out brain regions. (Figure 4.3). Differing views can be taken on brain anatomy using different slices, such as coronal (Figure 4.4), horizontal, or midsagittal (Figure 4.3), and reconstructed into a three-dimensional image (Figure 4.4).

2.0 A RANGE OF USEFUL TOOLS – MEASURING ELECTRIC AND MAGNETIC SIGNALS

2.1 Single-unit recording

Our most precise recording method today is single-neuron or 'unit' recording, using deep needle electrodes, sometimes implanted in the brain (Figure 4.5). Unit recording is often done so as to sample a dozen or even a few hundred neurons in a single study. Needle electrodes typically pick up axonal spikes, which are believed to be crucial in information processing and transmission. But unit recording has a sampling problem – how do we know that local spikes represent a whole region of the brain? It also matters whether cells are *excitatory* (making others fire more) or *inhibitory* (making others fire less). In addition, inserting a needle into the brain is invasive and potentially harmful – it requires surgery. It is therefore done only in experimental animals or in humans with medical conditions such as untreatable epilepsy, where exploratory surgery is required. We will see examples of each kind.

We can, in fact, record from single neurons that do important things, ever since Hubel and Wiesel (1962) were able to record single feature-sensitive cells in the visual cortex of the cat, an achievement for which they received a Nobel Prize in 1981. More recent work has recorded in medial temporal lobes (Figure 4.6). Like every method, electrical recording of axonal firing has its limitations, but it continues to be a major source of information. Neurons fire a maximum of 1000 Hz, but cortical neurons average about 10 Hz. We have no 'universal census' of cortical neurons, so we do not know with certainty how representative the small samples we can observe really are.

In many countries deep electrode recordings are allowed in primates, such as the macaque monkey, under suitable ethical constraints. The macaque brain has some striking similarities to human brains. Single-neuron recording in the macaque prefrontal cortex may show working memory phenomena. In a typical experiment, a

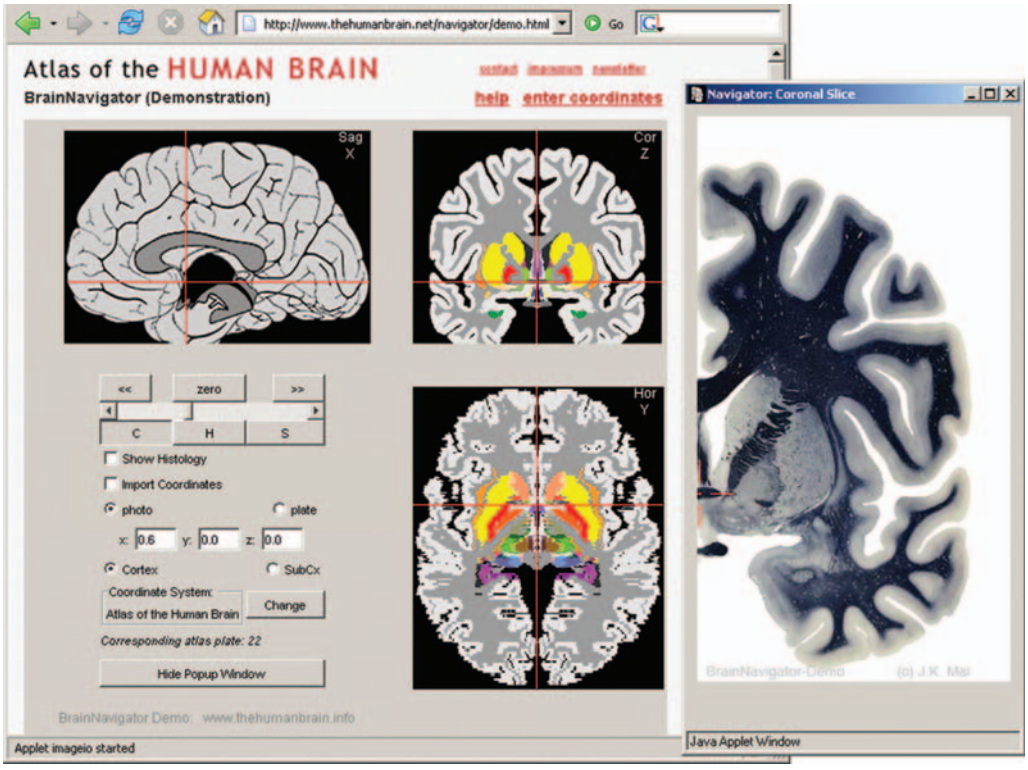


FIGURE 4.3 A brain navigation program. Brain navigation software allows the user to translate precise locations (in x, y, z coordinates) into brain locations. Notice the orientation of the standard slices. The x, y, z coordinates are known as the Talairach system (Talairach and Tournoux, 1988). Anatomical landmarks like the corpus callosum can be seen in the upper left display. *Source*: Mai and Thomas, 2006, with kind permission.

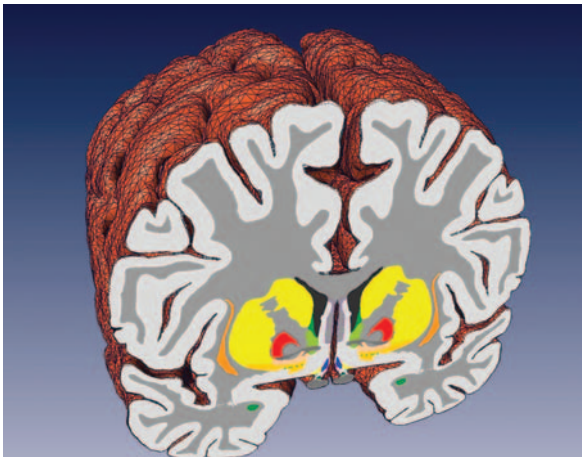


FIGURE 4.4 A coronal 'sausage slice'. A close-up in three dimensions from the Brain Navigator software. Yellow and Red colored shading show medial temporal regions in the left and right hemispheres. *Source*: Mai & Thomas, 2006, with permission.

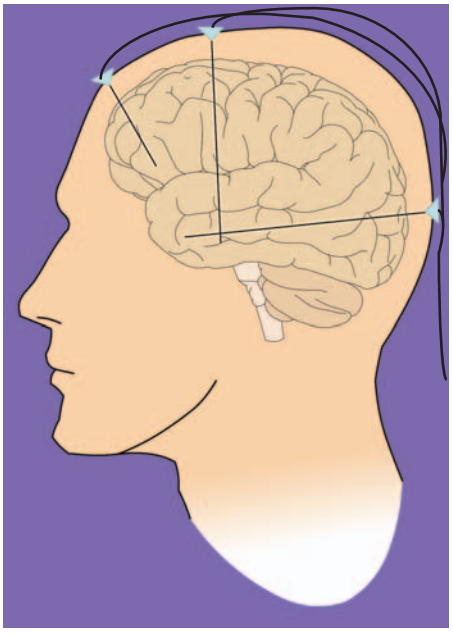


FIGURE 4.5 Single neuron recording deep in the brain. Intracellular and extracellular recording of single cells. Notice also the ability to stimulate single neurons, using the same electrodes. Single unit recording comes close to the desirable level of temporal and spatial resolution for brain recordings. It works very well in tracing circuits of neurons. However, this method does not allow us to track large-scale populations of neurons.

macaque is trained to fixate visually on a cross on a computer screen, and to perform a delayed response to a visual stimulus. The animal is trained to wait for a moment before looking in the direction where a stimulus appears; or alternatively, to look in the opposite direction. We can

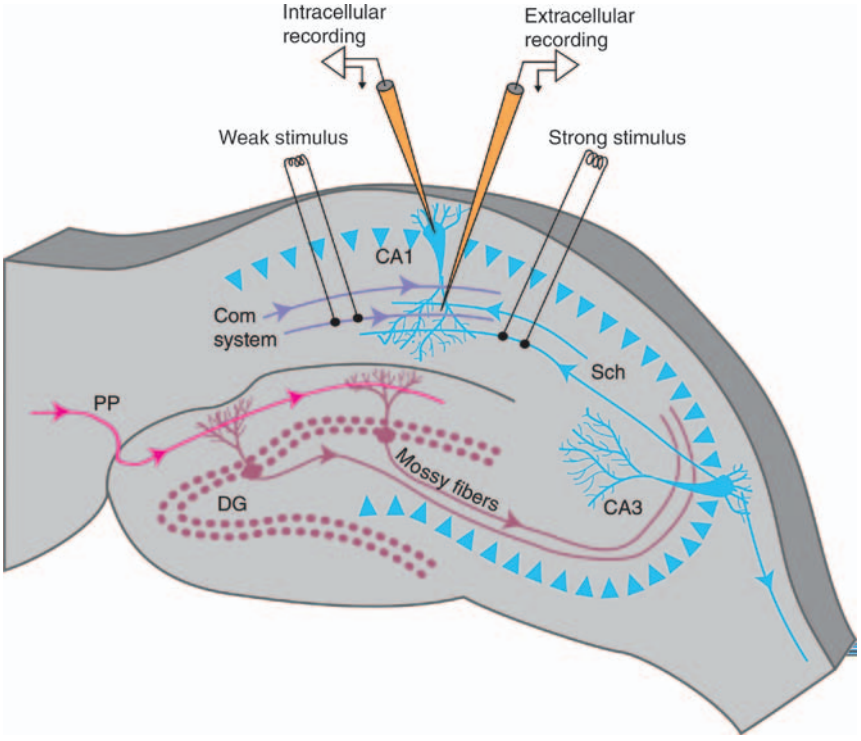


FIGURE 4.6 Unit recording in the hippocampus. Microscopic needles can be inserted into single neurons, or they can record extracellular electrical field potentials. The same electrodes can then be used to stimulate specific cells. The hippocampus contains regular arrays of neurons with distinct functions. *Source*: Squire *et al.*, 2003.

then record the activity of a single prefrontal neuron in the three phases: (1) the presentation of a visual stimulus; (2) the period when the monkey keeps the location of the visual stimulus in working memory; and (3) the response of looking in the direction of the stimulus after it disappears, or in the opposite direction. This is illustrated in Figure 4.7.

Depth electrodes have been used in humans. Typically, these electrodes are implanted before surgery in a patient who has otherwise untreatable epilepsy. The implants can determine where epileptic foci begin at the onset of a seizure, and where critical regions of the brain are located that must not be lesioned (Figure 4.8). In addition to localizing epileptic foci, depth electrodes have been used to assess areas in the brain that decode information such as sematic relatedness, shown in Figure 4.9.

How does recording in a single neuron relate to human perception? While a single cell cannot tell us much about human cognition, a recent experiment provided some intriguing results regarding conscious and unconscious visual perception (Figure 4.10).

While the spiking neuron is a plausible unit of brain activity, there are important alternative views. Some scientists believe that graded dendritic currents in each neuron may do useful information processing; some argue for subcellular processes inside the cell; others point to non-classical cells and synapses, which are known to be much more common than previously thought; others believe that glial cells participate in information processing; and many scientists believe that real brain processes only take place at the level of *populations* of neurons. Therefore, recording axonal spikes is important, but it may not be the only important thing going on. Obviously, it's a risky business to jump from a single neuron to more than 10 billion in the vast forest of the brain.

2.2 Animal and human studies cast light on each other

Non-human primates, such as macaque monkeys, have been extensively studied using single and multiple unit recordings. Much of what we know about vision, memory, attention, and executive functions comes from studies of the macaque (Figure 4.11).

How do brain regions in macaque correspond to human brain regions? While there are clearly some major anatomical differences, especially in frontal and parietal lobe regions, there remain some strong similarities between macaque and human brains (Figure 4.12).

Single unit studies in macaque do not just map sensory and perceptual features, they may also involve more cognitive aspects such as attention.

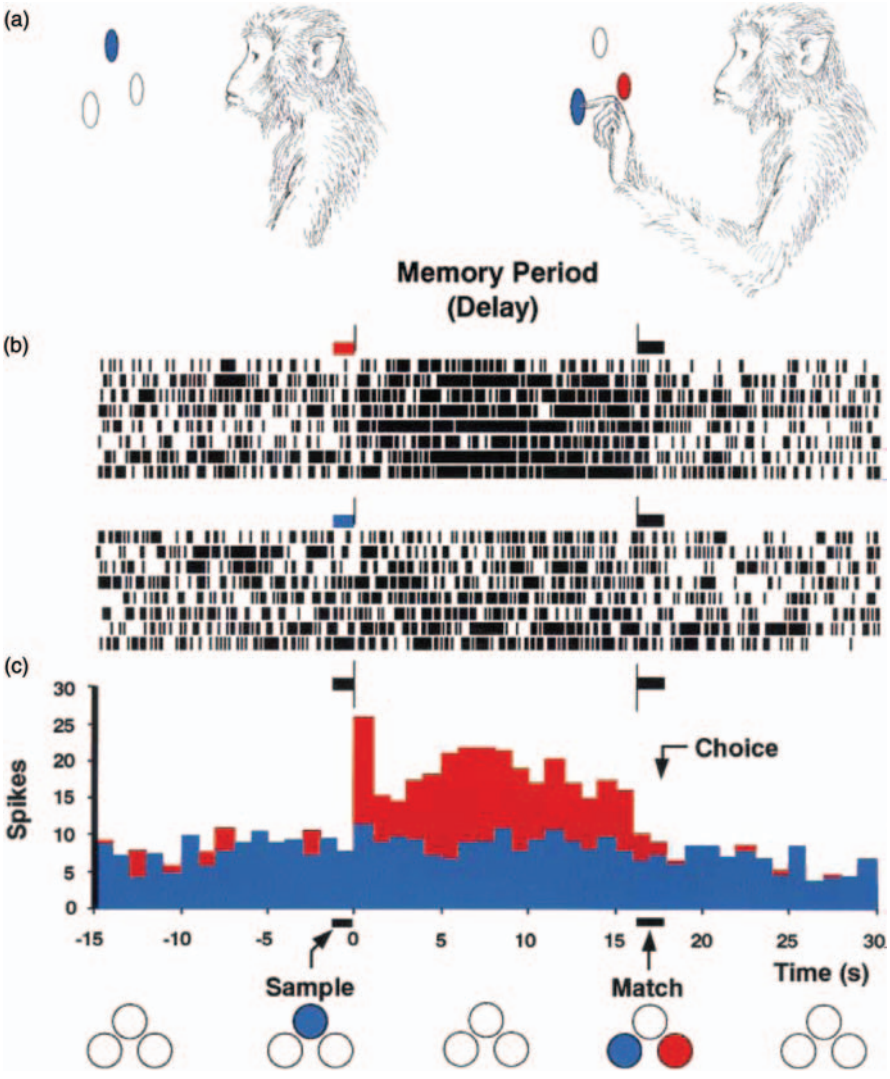


FIGURE 4.7 Working memory activity in single neurons. The macaque monkey is performing a working memory task called Delayed Match to Sample (DMTS). The 'sample stimulus' in this case is the blue dot in the display (a). Note that the monkey successfully presses the blue disk about 20 seconds later. Thus the animal can 'match to sample' even after the original stimulus is gone, implying that it must be kept in memory for a brief period of time. (b) shows a raster scan with neuronal spikes for each trial. Each horizontal set of small black lines is one trial. We can see that the neuron is firing faster in the Memory Period (Delay) compared to the preceding and following seconds. (c) shows a histogram of the firing of the neuron, located in the temporal lobe. Notice that the red columns in the Delay period indicate that the 'memory neuron' keeps firing even when the stimulus is not shown, but is held in immediate memory. This particular neuron has a background firing rate shown in blue, of 5-10 Hz, typical for cortical cells. However, between the sample stimulus and the successful matching choice, the neuron doubles its firing rate, shown in red. Such neurons are believed to be involved in the temporary stage of Working Memory contents. They often occur in the temporal and prefrontal lobes. *Source:* Fuster, 1997.

Single unit studies have provided us with a wealth of information regarding the encoding properties of neurons across cortical regions. However, neurons respond as ensembles, with complex networks of cells in multiple locations. How can we capture this type of dynamic brain response? An early technique for doing just that is presented in the next section: electroencephalography.

2.3 Electroencephalography (EEG)

The brain's large-scale electrical activity can be recorded through the scalp or on the surface of the cortex. Rather than picking up electrical activity direct from neurons, which are essentially tiny batteries, the electroencephalogram picks up the electrical field. The resulting brain

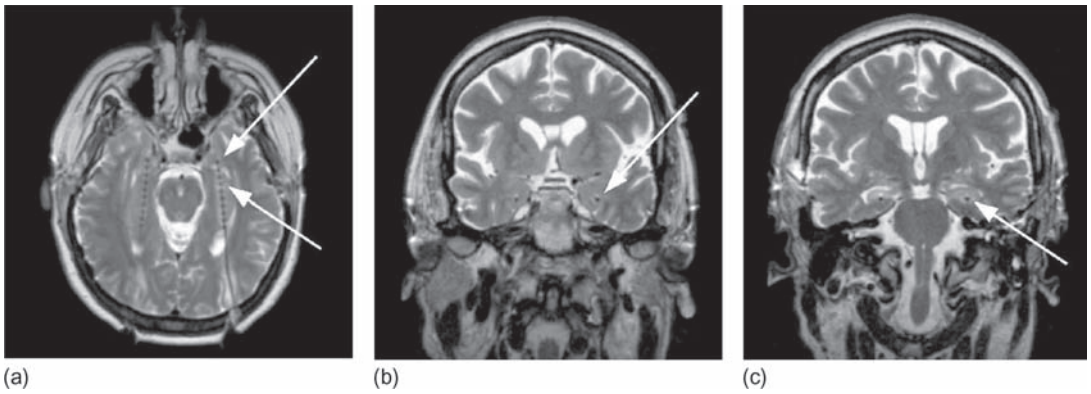


FIGURE 4.8 Depth electrodes in humans. While most single-cell recording is done in animals, human studies have been done when depth electrode recording is medically necessary. The arrows point to electrode placements in the temporal lobe. If you look carefully at the left MRI scan (a), you can see the electrode tracks, and the small holes in the rear of the scalp through which they were inserted. Neurosurgery like this is generally safe and pain-free, because the brain itself does not contain pain-sensing neurons. *Source*: Dietl *et al.*, 2005.

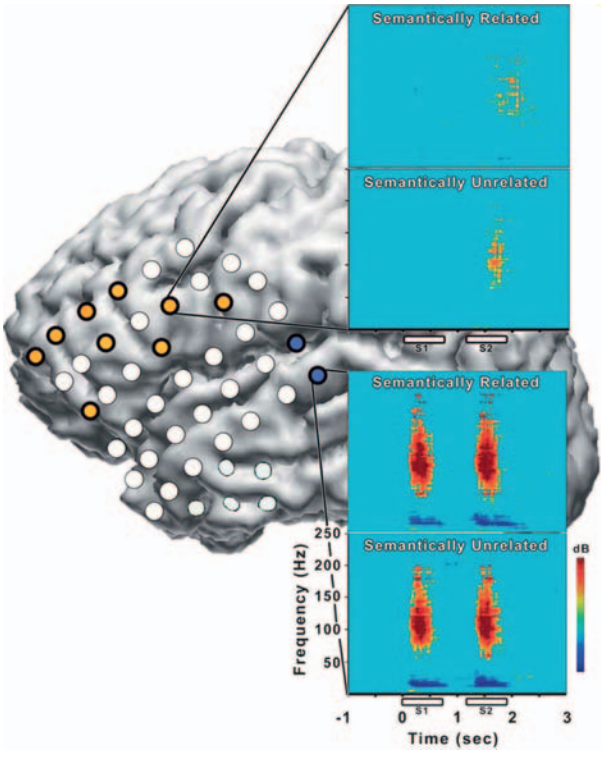


FIGURE 4.9 An example of the results from electrocorticographic (ECoG) recordings showing high-gamma oscillation (ERS – event-related Synchronization) which have been hypothesized to form the brain bases for 'binding' of information across sensory and cognitive domains. This figure shows the results of ECoG recordings during a lexical semantic processing task (deciding if two words were semantically related, such as 'knife' and 'fork'). Recording sites are shown color coded into white, yellow, and blue. Blue colored sites showed activation during auditory word stimuli but not during visual word stimuli, and so the authors described these sites as modality (auditory) specific. Further, these sites showed no modulation by semantic relatedness, which is shown in the lower two blue inset boxes. Yellow colored sites showed activation to both visual and auditory word stimuli, and hence the authors described these sites as modality-independent. These sites did show an effect of semantic relatedness, which is shown in the upper two blue inset boxes. *Source*: Crone, Sinai, & Korzeniewska, 2006.

record is referred to as an *electroencephalogram* (EEG) or electrical brain record. The EEG was discovered in 1929 by Hans Berger (Figure 4.15). Because electromagnetic waves propagate essentially instantaneously, EEG is highly sensitive temporally. However, EEG is quite selective, being more sensitive to neurons near the surface than to deeper neurons. EEG is picked up through layers of moist tissue, so that the original electrical activity is attenuated and distorted by the shape and conductive properties of the intervening cells. Some researchers believe that EEG is largely sensitive to the first layer of the cortex, which mainly consists of a tightly woven 'feltwork' of cortical dendrites (Freeman, 2004).

It is easiest to record EEG from the scalp, though it is sometimes recorded from electrodes placed directly on the cortical surface. Like unit electrodes, EEG is a relatively direct measure of the brain's electrical activity. But with tens of billions of cortical neurons firing about 10 Hz, we have several trillion electrical events per second. The raw EEG is therefore difficult to understand, and it was difficult to interpret before the advent of powerful computerized analysis.

However, when the EEG is averaged over a number of experimental trials and 'locked' to a specific zero point, like the onset of a stimulus, the averaged electrical activity yields elegant and regular waveforms. This event-related potential (ERP) is sensitive to large neuronal population activity that characterizes visual, auditory, and even semantic processes.

2.3.1 Sampling populations of neurons

The activity of large-scale populations and networks is another important level of analysis (Freeman, 2004; John, 2004). Spontaneous EEG shows different patterns of activation. The brain can operate with many different

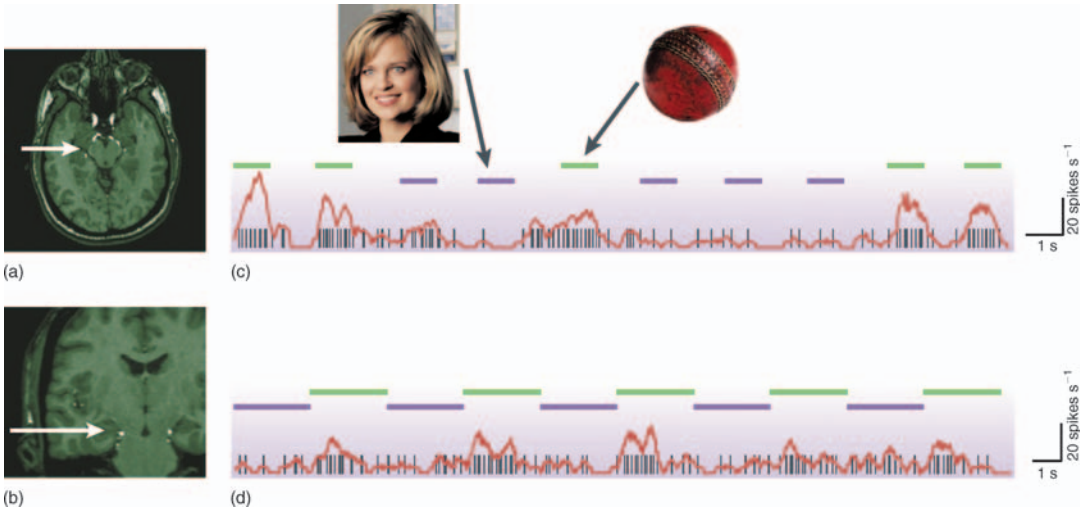


FIGURE 4.10 Human single cell recording and conscious perception. A remarkable experiment in which both conscious and unconscious stimuli were shown simultaneously to the two different eyes, using a variant of binocular rivalry (see Chapter 6). In the upper row (c), the woman's face is conscious but the ball is not; in the lower row (d), this is reversed. Peak firing rates, in red, during time periods marked by green horizontal bars, when the subject is indicating that the woman's face can be seen. The brain seems to determine which of the two simultaneous stimuli will become conscious when the signal reaches object recognition cortex. The electrode locations are shown on the brain scans on the left. *Source*: Rees *et al.*, 2002.

FIGURE 4.11 Monkeys have striking similarities to humans. Macaque monkeys are extensively studied because of apparent brain homologies (biological similarities) to humans. The macaque visual brain has been our best guide to the human visual cortex until very recently, when it became possible to study the human cortex more directly. Macaques also have emotional similarities to humans, close infant-mother bonding, and even prefrontal regions that resemble the human prefrontal cortex. Obviously, they do not have language and other species-specific human traits. *Source*: PLOS Biology open access journal.

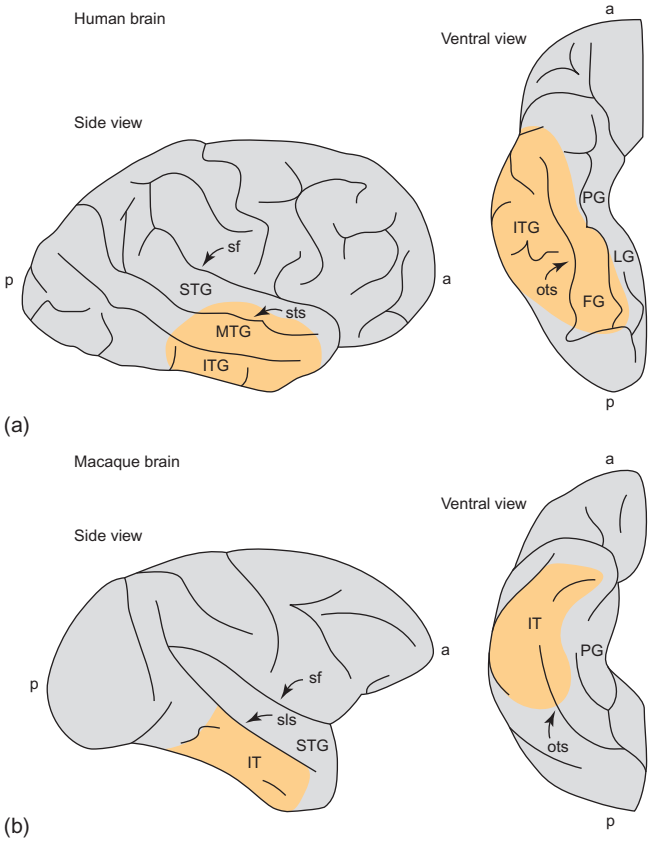


FIGURE 4.12 Brain homologies between humans and macaques. Above the human brain, and below, the macaque brain. The yellow areas are specialized in visual object recognition in both species. Both are shown from the right lateral perspective, looking to the right. (p) = posterior, (a) = anterior. The ventral view shows the bottom of the right hemispheres. *Source*: Squire *et al.*, 2003.

levels of interactivity. For example, during deep sleep, the raw EEG shows large, slow waves. This indicates that large groups of neurons are synchronized on a very large scale throughout the brain. When the subject wakes up, this slow pattern is replaced by small, rapid electrical waves, indicative of rapid and flexible information patterns of interaction in the brain. It is currently

BOX 4.1 ECoG: Direct brain recording

Even with fast-improving brain imaging techniques, the most direct evidence about the living brain still comes from *intracranial* electrical recordings. One reason is that the electrical signal strength in the brain is much greater than on the scalp – on the order of hundreds of *millivolts* rather than *microvolts*. Surface EEG is also filtered through a watery medium of brain tissue, skin, and muscle, the last with its own electrical activity. For example, when you frown, the muscles above your eyes contract, and along with it thin layers of muscle across the scalp stretch and adjust. Even eye movements have large effects on the scalp-recorded EEG. Thus, surface EEG recordings mix many electrical sources, as well as being filtered by layers of tissue. ECoG (electrocorticography) has an inherent advantage in signal-to-noise ratio. The biggest drawback is that ECoG requires invasive surgery. It is therefore never done without clear medical justification in humans. Numerous animal studies use ECoG or depth electrodes and still provide much of the basic evidence about brain activity.

Wilder Penfield and his colleagues pioneered electrocorticography in humans in the 1950s. Epileptics with uncontrolled seizures can benefit from surgical removal of seizure-causing patches of the brain. ECoG recording can show where such "epileptogenic foci" are located. In addition, the surgeon needs to know which areas to avoid cutting, because they are vital for perception and language. ECoG studies are relatively safe and practical prior to surgery. Probing the cortical surface is generally pain-free, because the cortex does not have pain receptors. The scientific benefits have been very important (see Chapter 8). While animal studies have laid the foundations for direct brain recording, ECoG studies in conscious humans are helping to uncover the neural basis of language, conscious perception, and voluntary control.

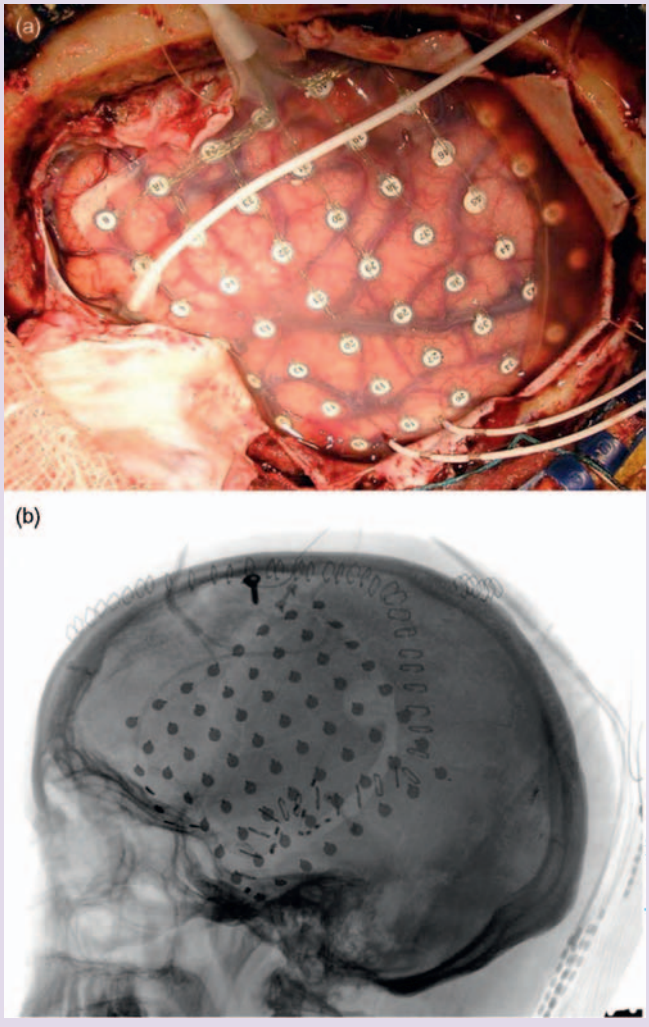


FIGURE 4.13 (a) A surgically exposed cortex with an 8×8 electrode grid placed directly on the surface. The electrodes (white circles) are mounted on a transparent plastic square that is overlaid on the left hemisphere. Notice that the grid covers part of the temporal lobe, a common source of seizure activity. It also samples the receptive language region of the left hemisphere (Wernicke's area), as well as Broca's area (the left inferior frontal gyrus), which controls language production. The left hemisphere is dominant for language in most people, and the electrodes are therefore placed over the most critical locations. (b) An X-ray radiograph of the same patient, superimposed on a structural MRI of the lateral brain. *Source*: Dalal *et al.* (2008).

(*Continued*)

BOX 4.1 (Continued)

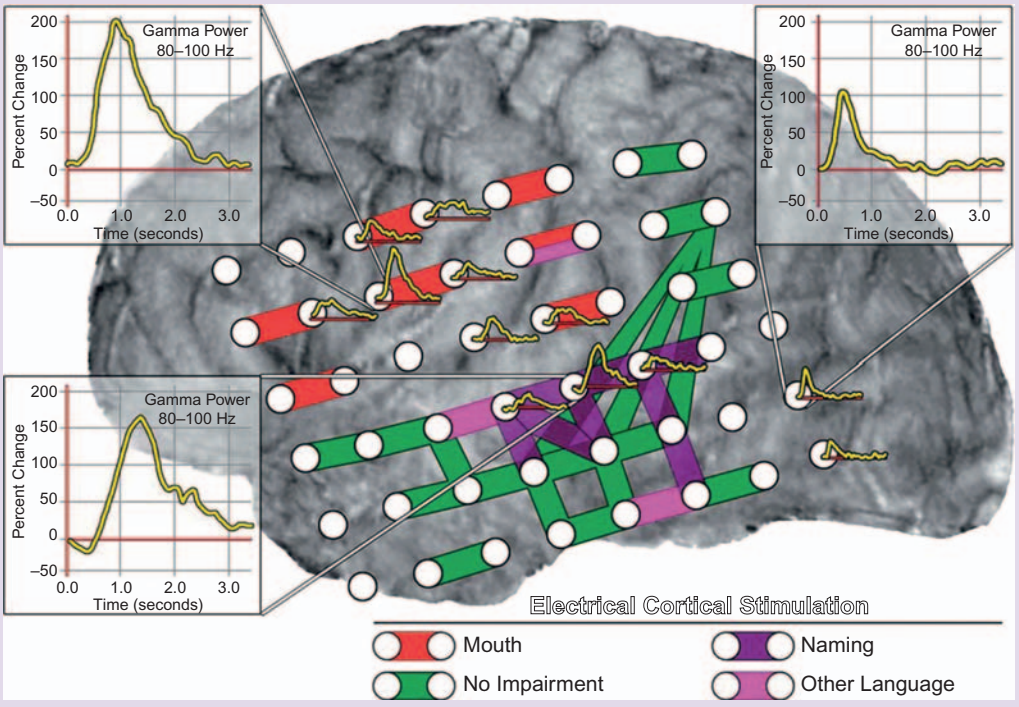


FIGURE 4.14 The results of an ECoG study of an epileptic patient, shown over an MRI of the lateral brain. The three inset graphs show a fast increase in high gamma activity (80–100 Hz) immediately after a picture with an object to be named is presented. The patient is asked to name the object, and the electrical activity is averaged over all presentations. The colored strips show which electrode pairs were used for cortical stimulation, which typically interferes with the functioning of the underlying cortical area. The red and purple strips mark places where electrical stimulation interfered with picture naming, mouth movements, and other language responses. The green strips indicate electrode pairs for which electrical stimulation caused no task interference. *Source*: Crone, Sinai, & Korzeniewska, 2006.

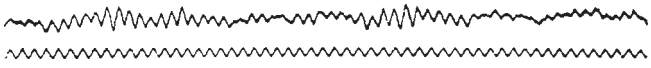


FIGURE 4.15 The first EEG. This historic EEG signal was recorded by Hans Berger in 1929, using a single pair of electrodes, on the scalp. Above, an EEG signal recorded on Berger's son, showing alpha activity (the regular sine wave in the upper trace). The lower trace is an electrical timing wave of 10 Hz. *Source*: Gottesmann, 1999.

believed that cortical neurons do not fire at different average rates during deep sleep compared to waking, but rather that waking EEG allows a far greater amount of interactive processing. Sleep is not a passive state, therefore, but a different operating mode of the brain, with its own functions. One of these is believed to be the consolidation of memories based on waking experiences (Hobson and Stickgold, 1995).

The standard method for analyzing highly complex EEG is Fourier analysis, named after the French mathematician Pierre Fourier, who showed that any complex signal can be decomposed into sine waves with differing amounts of power (density) in each frequency range (Figures 4.16).

The 'raw' (unprocessed) EEG shows visibly different waveforms like alpha, beta-gamma, theta and delta. However, raw EEG is believed to be a combination of many different kinds of activity. Using mathematical analysis, we can decompose these complex and noisy waveforms into frequencies components. This is not unlike taking noisy radio static and decomposing it into frequency bands – which is exactly what we do by tuning to a specific radio station. The analyzed EEG shows that certain tasks may show a specific rhythm, such as alpha or gamma, in specific regions of the brain. This is illustrated in Figures 4.16 and 4.17. Some of these typical frequency bands are shown in Table 4.1.

The classical EEG waveforms can be picked up directly, from the 'raw' or unanalyzed EEG. Notice especially the

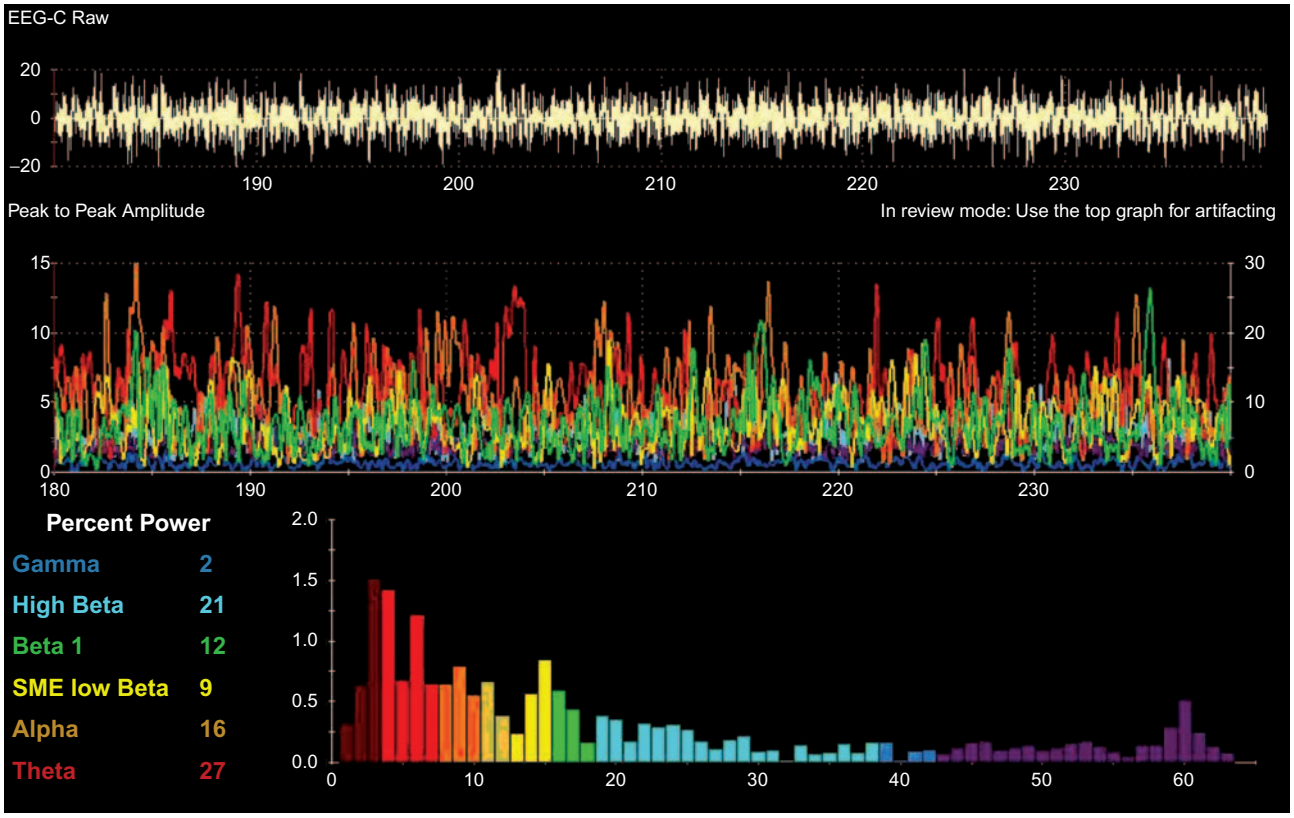


FIGURE 4.16 Regular rhythms in different parts of the brain. A method called Fourier analysis allows us to decompose the density (or power) of regular wave forms that are buried in noisy EEG (see Table 4.1). The graphs show the resulting power curves. According to this source, the greatest alpha density is found over the occipital cortex, while the greatest theta density is over the frontal cortex. Theta is thought to involve hippocampal-frontal interactions during long-term memory retrieval. Gamma is found widely through the brain, and is believed to reflect functional interactions between different regions during the conscious state. The colors correspond to different frequency ranges. *Source*: From Zoran Josipovich, with permission.

widespread, low-amplitude beta and gamma activity typical of waking conscious states. The opposite state occurs in deep sleep, when the EEG is slow, high in amplitude, and much more regular. Other unconscious states show similarities (Baars *et al*., 2004). Alpha activity may be seen over the occipital cortex when subjects are in a relaxed but alert state.

As mentioned, while EEG has a millisecond time resolution, its spatial resolution is rather poor. It is very difficult to locate the electrical source of the EEG signal. It helps to increase the number of electrodes and to use sophisticated analytical methods. However, EEG gives us little information about brain regions deep beneath the cortex. Since subcortical regions like the thalamus are very important, EEG seems to have inherent limits.

Early uses of EEG were to evaluate brain responses during sleep and dreaming states (Figure 4.15). New improvements using high-density arrays of electrodes have enabled scientists to make better, more detailed measurements of brain responses.

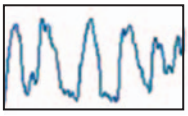
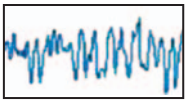
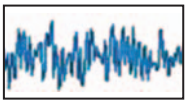
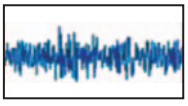
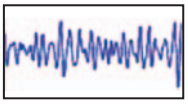
An important aspect of EEG recording is to measure the evoked potential (ERP) that occurs in response to specific stimuli. To improve the signal to noise, these responses are averaged over many trials.

For example, visual ERPs have been measured to investigate the time course of explicit memory processing (Figure 4.18). The ERP is sensitive to many factors that are important in human cognition, such as hearing your own name or listening to music (Figure 4.19). EEG reveals brain patterns during sleep and waking, abnormalities during diseases like epilepsy, and even the brain areas that respond to music. A more recent technique, magnetoencephalography (MEG), is highly related to EEG and has provided new ways to image the human brain.

2.4 Magnetoencephalography (MEG)

Magnetoencephalography (MEG) measures the magnetic field produced by electrical activity in the brain (Figure 4.20). Its spatial resolution at parts of the

TABLE 4.1 EEG frequencies and their associated functions

Name and example	Description
Delta 	Delta is the slow wave characteristic of deep, unconscious sleep. It is less than 4 Hz, and similar EEG frequencies appear in epileptic seizures and loss of consciousness, as well as some comatose states. It is therefore thought to reflect the brain of an unconscious person. The Delta frequency tends to be the highest in amplitude and the slowest waves. Delta waves increase in relation to our decreasing awareness of the physical world.
Theta 	Theta activity has a frequency of 3.5 to 7.5 Hz. Theta waves are thought to involve many neurons firing synchronously. Theta rhythms are observed during some sleep states, and in states of quiet focus, for example meditation. They are also manifested during some short term memory tasks, and during memory retrieval. Theta waves seem to communicate between the hippocampus and cortex in memory encoding and retrieval.
Alpha 	Alpha waves are those between 7.5 and 13Hz that arise from synchronous and coherent (in phase) electrical activity of large groups of neurons in the human brain. They are also called Berger's waves in memory of the founder of EEG. Alpha waves are predominantly found to originate from the occipital lobe during periods of relaxation, with eyes closed but still awake. Conversely alpha waves are attenuated with open eyes as well as by drowsiness and sleep.
Beta 	Beta activity is 'fast' irregular activity, at low voltage (12–25 Hz). Beta waves are usually associated with normal waking consciousness, often active, busy, or anxious thinking and active concentration. Rhythmic beta with a dominant set of frequencies may be associated with various pathologies and drug effects. Beta is usually seen on both sides of the brain in symmetrical distribution and is most evident frontally. It may be absent or reduced in areas of cortical damage.
Gamma 	Gamma generally ranges between 26 and 70Hz, centered around 40Hz. Gamma waves are thought to signal active exchange of information between cortical and subcortical regions. It is seen during the conscious waking state and in REM dreams (Rapid Eye Movement sleep). Note that gamma and beta activity may overlap.

cortical surface is now approaching a few millimeters, while its temporal resolution is in milliseconds (Figure 4.21).

Because of the physics of magnetism, MEG is highly sensitive to dendritic flow at right angles to the walls of the sulci (the cortical folds), but much less sensitive to the bottom. MEG has excellent temporal resolution and somewhat better spatial accuracy than EEG.

Like any other method that measures brain activity, MEG results must be superimposed upon a structural image of the living brain. MEG uses a process called *magnetic source imaging* (MSI) to co-register the magnetic sources of brain activity onto anatomical pictures provided by MRI. In this way, MSI combines the high spatial resolution of MRI with the high temporal resolution of MEG. MSI techniques are used before brain surgery, to pinpoint brain regions with vital functions that must be protected during surgery.

MEG has the advantage of being entirely silent and non-invasive. As we will see, MRI is quite noisy, and of course depth electrodes require surgery. Thus, MEG is attractive for use with children and vulnerable people.

2.5 Zapping the brain

We have discussed techniques for non-invasive recording of brain signals, but what if you could evoke neural activity in a safe fashion? Such a method would be especially useful to test causal relationships between evoked neural activity and cognitive functions.

Early work on direct electrical brain stimulation began with Wilder Penfield, a neurosurgeon at the Montreal Neurological Institute (Figures 4.22 and 4.23). Penfield and his colleagues treated patients with intractable epilepsy. In open brain surgery, patients can remain awake and responsive, since only local anesthetic is needed at

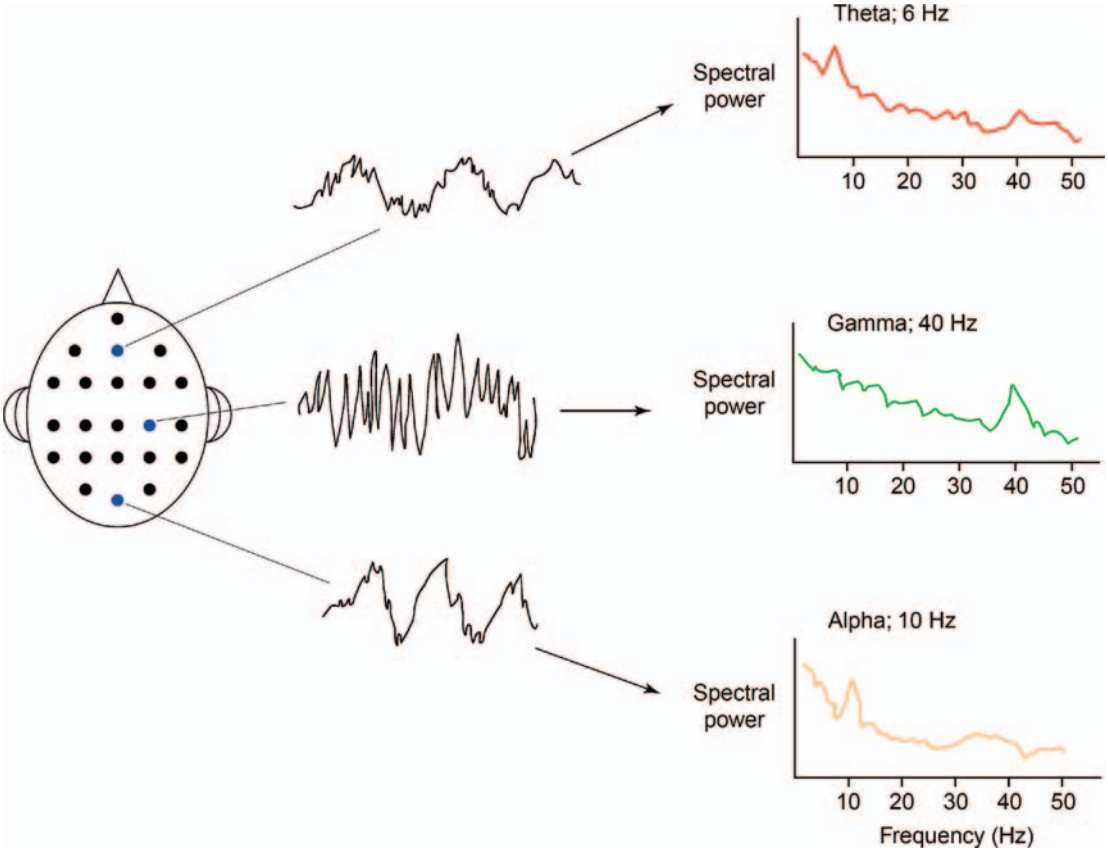


FIGURE 4.17 Regular waveforms from different brain regions. Three waveforms with important cognitive functions are alpha, classically associated with relaxed and alert states, and often found over the occipital cortex. Frontal theta is now believed to reflect interactions between the hippocampus and cortex. Finally, gamma activity is often thought to reflect transient large-scale assemblies of neurons associated with conscious percepts and other cognitive processes. 'Spectral power' is the area under the curve of the frequency graph, and reflects the physical energy in each frequency band. *Source*: Ward, 2002.

the site. There are no pain receptors in the brain itself, so that the cortex brain can be stimulated and operated upon without general anesthesia. This is a vital part of the operation, because surgeons need to map out brain regions that are needed for normal functions. Epileptic foci, which trigger major seizures, can then be cut out with the least side effects.

2.5.1 *A safe way of interfering with brain function: transcranial magnetic stimulation (TMS)*

It is now possible to stimulate brain lesions in healthy subjects. Without cutting a person's brain, we can alter the brain's level of activity very locally. Brief magnetic pulses over the scalp either inhibit or excite a small region of cortex. For example, if you stimulate the hand area of the motor cortex, the subject's hand will suddenly move and twist. Applying an inhibitory pulse over the same area will cause subjects to have difficulty moving their hands. This is called *transcranial magnetic stimulation* (TMS) or, as one leading researcher has called it, 'zapping the brain' (Cowey and Walsh, 2001). TMS (Figure 4.26) appears to be generally safe. By applying TMS, we can now test causal hypotheses about the contribution of specific brain regions to complex cognitive processes. Since the TMS works at the millisecond scale, it is also possible to study how rapid waves of processing develop.

Overgaard *et al*. (2004) used TMS to explore visual consciousness. Subjects were given simple geometric shapes, like triangles, squares, and circles, in three different colors (red, green, and blue). The stimuli were presented in one of three locations on the screen. All the shapes were shown long enough to be seen by all subjects. The researchers then applied a TMS inhibitory pulse to the mid-temporal region in both hemispheres, roughly just in front of each ear. If the pulse was applied about 120 milliseconds after the stimulus

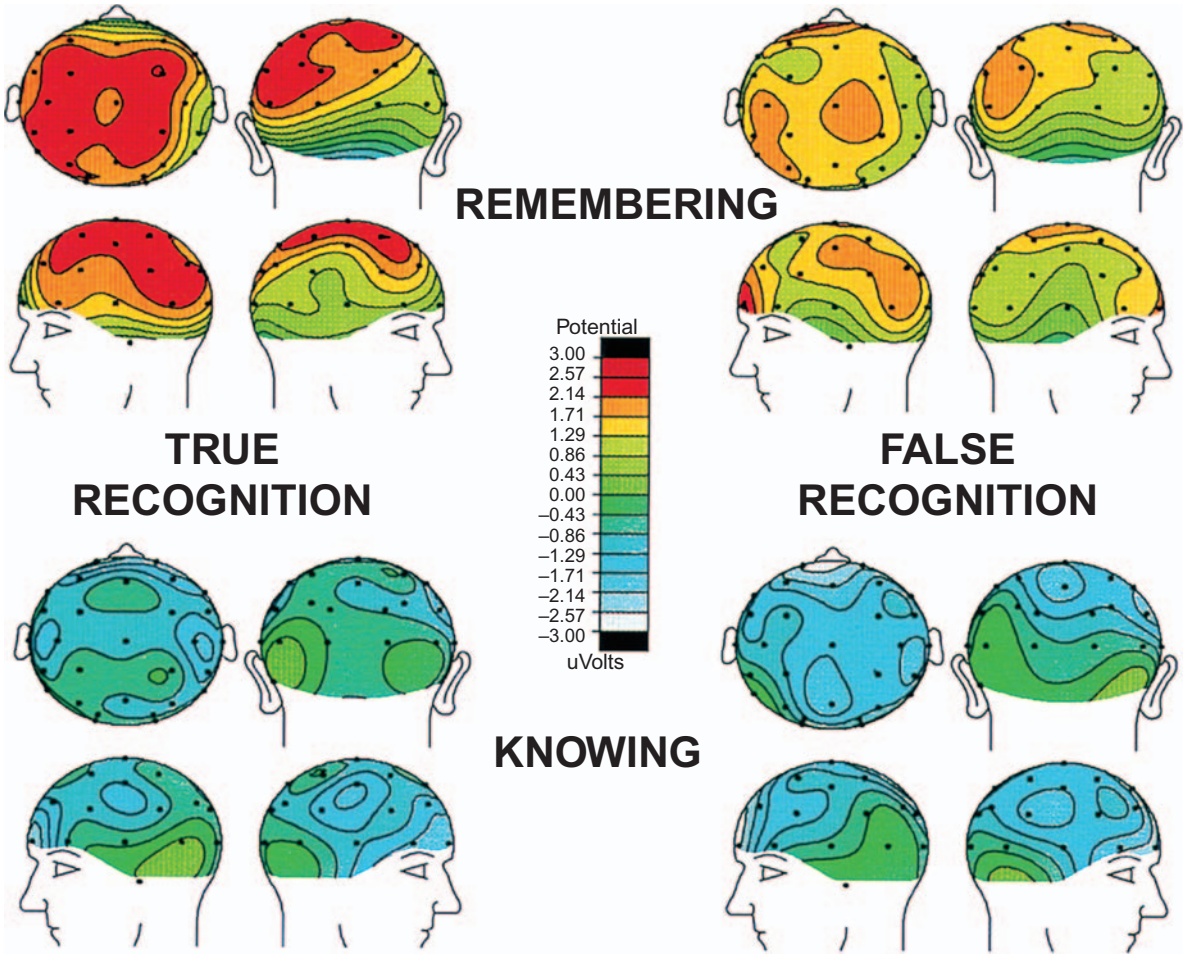


FIGURE 4.18 Evoked potentials are often shown by topographical maps of averaged voltages across the scalp. Redder colors are higher voltages. In this case, explicit remembering of conscious memories evokes much higher ERPs than the 'feeling of knowing' for the same memories. Brain activity is not as well localized with ERPs as it would be with PET or fMRI. *Source:* Düzel *et al.*, 1997.

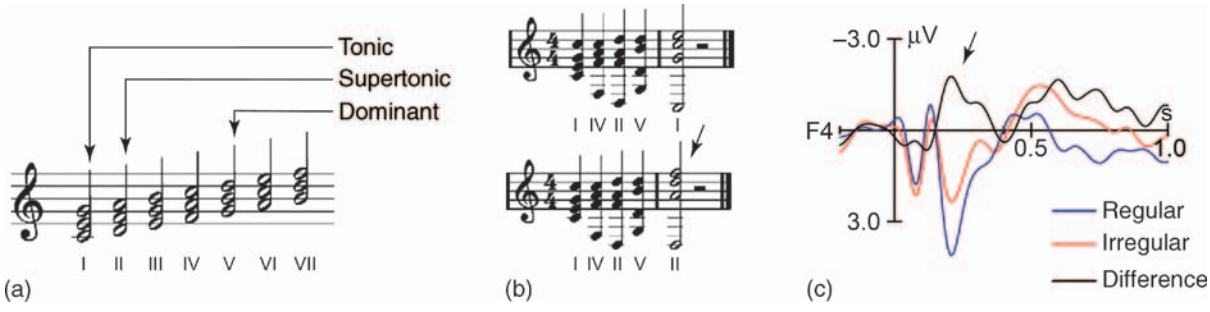


FIGURE 4.19 Evoked potentials to musical meaning. Regular musical sequences are perceived as more pleasant, and show a larger evoked potential (see the arrow in the graph, (c)). Irregular musical sequences evoked a very different brain response. *Source*: Koelsch and Siebel, 2005.

was shown, there was a dramatic drop in subjects' awareness of the stimuli. They no longer had a clear perception of the figures, but either a vague impression that something had been shown, or none at all.

Interestingly, when subjects were asked to guess the stimuli, they all showed normal performance. Yet they did not report being conscious of the stimuli. The stimuli must still have been detected (unconsciously) to

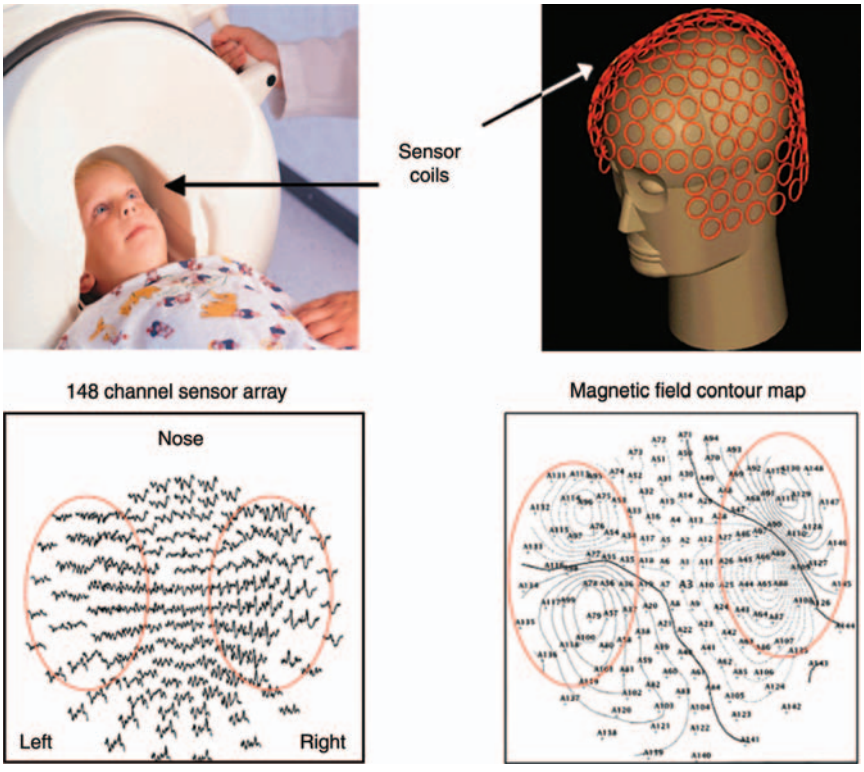


FIGURE 4.20 MEG is silent and non-invasive. MEG is easy for young children to tolerate, as long as they can stay relatively still. The pictures at the bottom of the figure show the vector fields of the MEG over the head of the subject. *Source*: 4D Neuroimaging, San Diego.

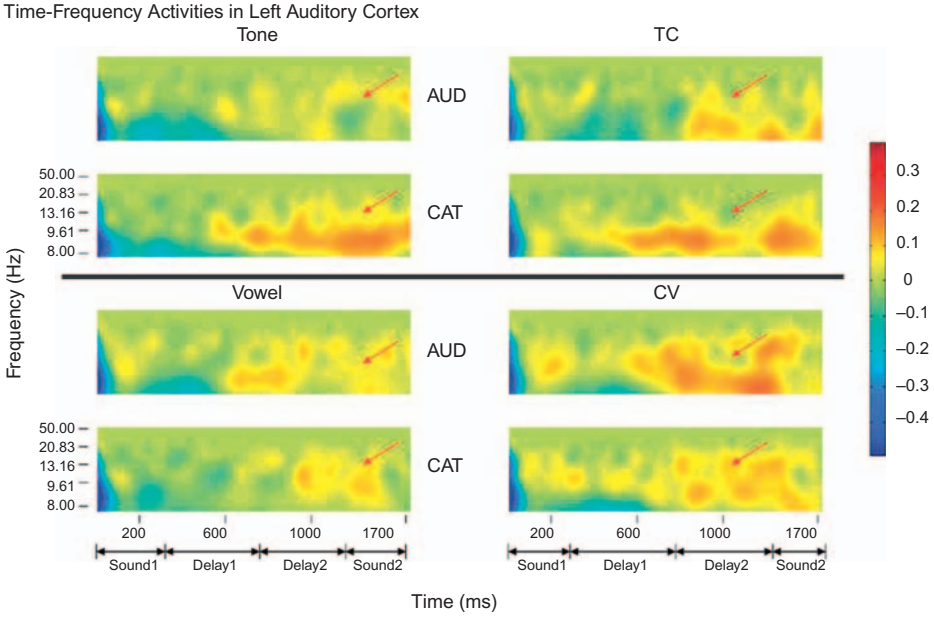


FIGURE 4.21 An example of a wavelet analysis of MEG data in response to speech and non-speech sounds. The non-speech sounds consisted of steady-state tones, tonal contours (TC) which contained dynamic changes; speech sounds consisted of steady-state vowels and consonant vowel (CV) syllables which contained dynamic changes. Using a wavelet analysis, with time on the x-axis and frequency on the y-axis, and color denoting the level of activity, the authors investigated neural activity by stimulus contrasts and task (AUD, the subjects decided if two sounds were exactly the same, CAT, the subjects decided if two sounds were in the same category). Results: high levels of activity in the alpha (8-13 Hz) band, shown in red on the wavelet plots.

FIGURE 4.22 Wilder Penfield. Penfield and colleagues devised open-brain neurosurgery for untreatable epilepsy in the 1950s. *Source*: Adelman and Smith, 2004.

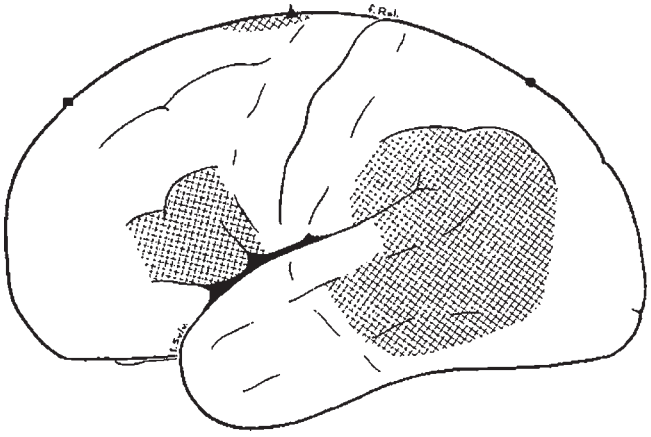


FIGURE 4.23 Penfield's map of brain regions where electrical stimulation interferes with language. Penfield and Roberts discovered that electrical stimulation in the indicated regions interfere with language production or perception. Notice how closely these regions correspond to the classical Broca's and Wernicke's patients studied a century before. *Source*: Adelman and Smith, 2004.

FRONTIERS OF COGNITIVE NEUROSCIENCE

A conversation with Michael Rugg: Neuroimaging correlates of cognition

FIGURE 4.24 Michael D. Rugg, PhD, Department of Neurobiology and Behavior and Department of Cognitive

The emergent field of cognitive neuroscience provides exciting new and ever-changing ways to investigate the neural correlates of human thought and cognition. An influential leader in this field is Dr. Michael Rugg, Professor in the Department of Neurobiology and Behavior and Director of the Center for the Neurobiology of Learning and Memory at the University of California, Irvine. We sat down with Dr. Rugg and asked him how his approach to investigating the neural correlates of human memory have shifted over the past decade, and how he thinks the field will continue to shift in the next. Here are some highlights of that conversation. (CBC: editors Bernard J. Baars and Nicole M. Gage; MR: Michael Rugg).

CBC: Let's begin with a little history: with respect to your own body of work, how has your approach changed in the past decade as a cognitive neuroscientist?

MR: For me, I think it coincides with the availability of brain imaging methods that allow one to directly identify the neural populations and the neural circuits that are engaged during different cognitive tasks. When I first started in what we now call cognitive neuroscience, it was primarily composed of people who wanted to use brain measures to dissociate cognitive processes. Pretty well the only method available was EEG-based measures, and so at that time there was a lot of emphasis on simply using neural measures to dissociate different kinds of cognitive processes. The logic is: if you have two experimental conditions that give rise to very different patterns of brain activity that clearly don't come from the same 'bits of the brain', then that's reasonable evidence, given certain assumptions, that you may have dissociated two different cognitive processes.

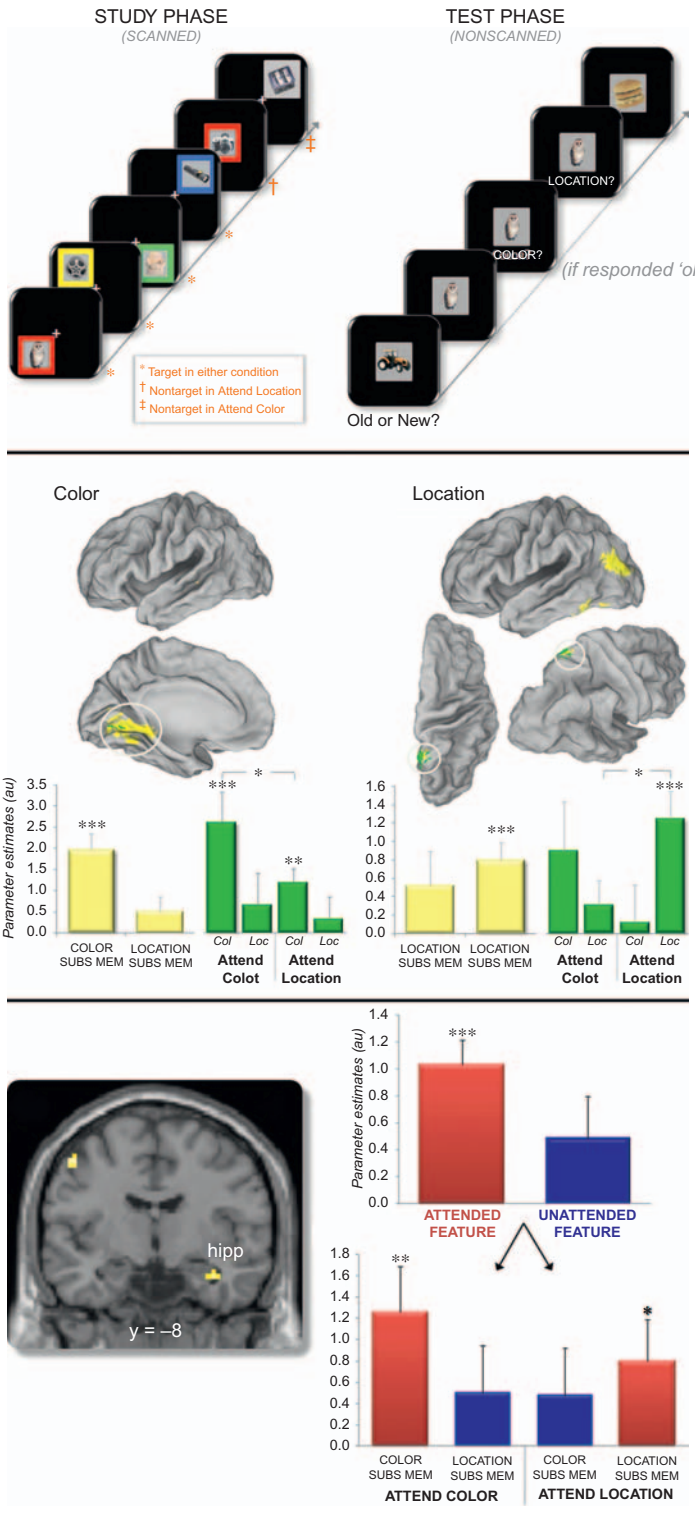


FIGURE 4.25 An example of the experimental design used in Dr. Rugg's fMRI memory experiments. In this experiment, they were investigating the role of attention for color and location during a memory task. *Top*: Experimental design. *Left*: The study materials, showing the use of color and location cues during the Study Phase when subjects were scanned. *Right*: The study materials used during the Test Phase, where color and location cues were removed. *Middle*: Feature-specific subsequent memory effects. *Left*: Memory effects selective for color (displayed in yellow) are shown on a standardized brain. A subset of these color-selective memory effects was additionally modulated by attention to color (overlaid in green). *Right*: Memory effects selective for location (yellow) also show brain areas that are modulated by attention to location (green). *Bottom*: Medial temporal lobe encoding attended contextual information. *Left*: A right hippocampal region shows memory effects for contextual information that is selectively attended (regardless of which feature is attended) and does not show significant effects for information that is not attended. *Right*: Graphs show estimates of the effects for attended vs. unattended trials, then broken down by color and location. *Source*: Uncapher and Rugg, 2009.

And then with the shift to first PET and then fMRI, the same logic could be applied but now you have much more confidence in where in the brain these differential patterns of activation are occurring. You start to think much more directly about what different parts of the brain might be doing to support these different hypothetical cognitive processes: instead of using brain data as (more or less) a substitute for – or a complement to – reaction times or error rate, or any other behavioral measure, the data actually become a *source of information* in its own right. Now you may ask: why is it that certain kinds of retrieval operations engage different parts of the parietal cortex relative to other kinds of retrieval operations? What is it that parietal cortex might be doing that means that it is more interested in only some of these operations, and what does that tell us theoretically about the neural networks that support different kinds of cognitive processes?

CBC: Investigating complex neural systems such as memory presents a challenge for designing experiments that allow you to tease apart subtle but important aspects of a complex system. What is your approach to this?

MR: I think one of the other things that has become clear is that you can't study memory – or the neural correlates of memory – without some reasonably tight, well-articulated preexperimental theory about how you think memory is organized and how you think your task is tapping into different kinds of memory processes. This is no different from any other area of cognition, but it is particularly painfully obvious in memory that you can't simply stick someone in the scanner and say 'I'm going to study memory.' You need to have a reasonably well-articulated cognitive or functional theory of memory which guides your experimentation and your interpretation. One of the big areas of controversy at the moment in the cognitive neuroscience of memory is really about this: it's not about the data, at all, the data are reasonably agreed-upon. It's about the *interpretation* of the data and that comes from people holding different preexperimental premises about how memory is organized, how it should be measured, and what the criteria are for saying that you have separated out differing memory processes from a behavioral point of view. Differing labs may have similar sets of data to other labs but their interpretation of those data may be starkly different: the different interpretations, then, depend not on the neuroscience, but on the experimental psychology.

CBC: Let's look forward now, what do you see as upcoming changes in the approach to investigating the cognitive neuroscience of human memory?

MR: I think it's a question of getting more sophisticated in terms of the behavioral procedures and also thinking much more deeply about what the theoretical implications are of differing patterns of findings and trying to see them from more than one theoretical perspective. The other thing that is clear – and this comes to a methodological point – it's probably no longer helpful to try to characterize memory-related activity in broad terms like 'hippocampus' vs. 'non-hippocampus', 'entorhinal cortex' vs. 'parahippocampal cortex', and so on. The reason being that these are highly differentiated structures and it's probably a gross oversimplification to think that just because two tasks both engage the hippocampus, for example, they must, in some sense, both be sharing some low-level cognitive operation. We now have the ability with MRI to do high resolution functional neuroimaging of the hippocampus at a level that allows us to identify patterns of activity in hippocampal subfields. There are people, for example, now claiming to see dissociable patterns of activity in, say, dentate gyrus and CA1 vs. CA3. So how can you say, then, that those two tasks both engage the hippocampus and thus they are doing the same thing? In other words, the level of resolution, if you like, with which one can dissociate the neural correlates of cognition is getting finer and finer. That is going to change the way people conceptualize 'neural dissociations' and 'cognitive dissociations.'

permit accurate detection. Yet no subjective experience of the words was reported.

Now let's turn to methods for investigating the brain that use spatial mapping techniques to explore both brain anatomy and function.

3.0 FUNCTIONAL NEUROIMAGING: A BOLD NEW WORLD

EEG and MEG measure brain activity fairly directly. Other neuroimaging measures use indirect measures,

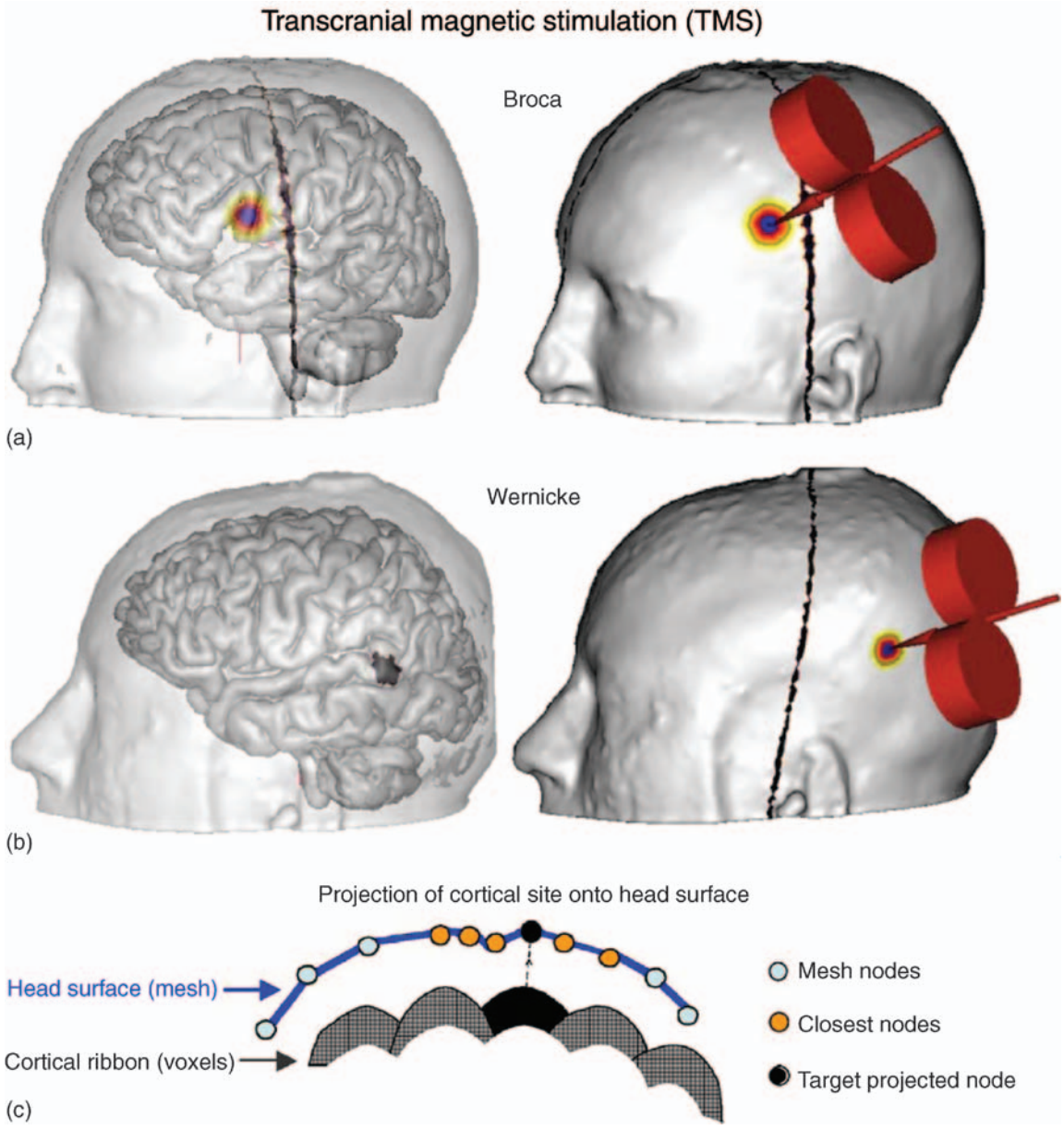


FIGURE 4.26 Magnetic brain stimulation is not surgically invasive. Brain stimulation can be applied without surgery. In this example, it is being applied over Broca's and Wernicke's areas in the left hemisphere of the subject. TMS appears to be safe at mild levels of intensity and frequency. It allows causal hypotheses to be tested in brain experiments, a major methodological advance. *Source*: Andoh *et al.*, 2006.

such as blood flow or regional oxygen level. Currently, the most popular method is fMRI (functional magnetic resonance imaging) (Figure 4.27) and especially the kind that measures the oxygen level of the local blood circulation (called BOLD, for blood-oxygen level dependent activity, see Figures 4.28 and 4.29).

When neurons fire they consume oxygen and glucose and secrete metabolic waste products. An active brain region consumes its local blood oxygen supply, and as oxygen is consumed we can see as a small drop in the BOLD signal. In a fraction of a second the loss of regional oxygen triggers a new influx of oxygen-rich blood to that region. Here, we see a recovery of the signal. However, as the compensatory mechanism overshoots, flooding more oxygenated blood into the area than is needed, we also see that the signal rises high above the baseline. Finally, as unused oxygen-rich blood flushes out of the region,

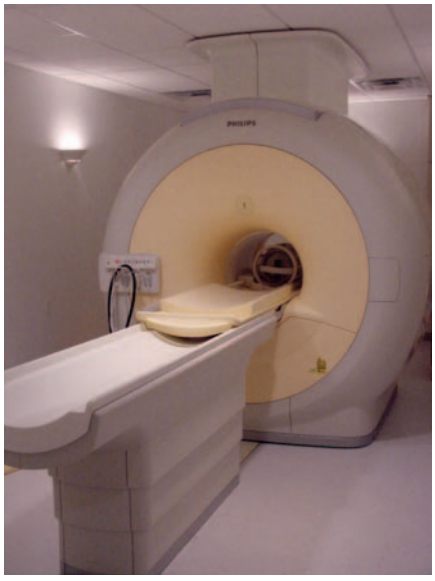


FIGURE 4.27 How the MRI equipment looks to the subject. Most fMRIs are taken with the subject lying down. Today's MRIs are still very noisy, as the electromagnetic coil is switched on and off. Small visual displays may be used to present stimuli, or headphones for auditory stimuli. Because the machine generates high-intensity magnetic fields, no metal objects like pens or even paperclips can be taken into the examination room. *Source:* Sharma and Sharma, 2004.

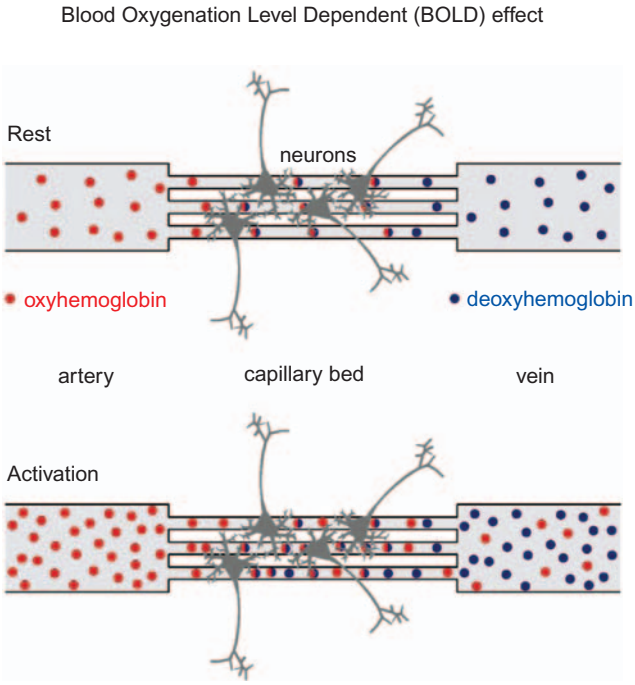


FIGURE 4.28 The basis of functional MRI (fMRI). The most popular brain imaging method today is probably fMRI, which is less expensive than PET, and provides a good localization of brain activity. fMRI is an indirect measure of neuronal regional activity, as shown here. Neuronal activation increases the oxygen demand of neurons and related cells, leading to additional blood flow carrying oxygen molecules to the region. This can be measured using BOLD – Blood Oxygen Level Dependent activity. Since neurons start firing several seconds before additional BOLD activity starts, there is a built-in lag time in fMRI. *Source:* Dogil *et al.*, 2002.

we can see a drop in the BOLD signal, back to the baseline.

Thus, as the oxygen content of blood produces changes in the BOLD signal, we can measure neural activation indirectly. The BOLD signal comes about six seconds after the onset of neuronal firing. The relationship between neural activation and the BOLD fMRI signal is shown in Figures 4.28 and 4.29.

Positron emission tomography (PET) was developed much earlier than MRI or fMRI, and provides a measure of metabolic brain activity (Figure 4.30). PET is used less often for research today, because it is very expensive, requiring a cyclotron. It also requires subjects to be injected with a radioactive tracer. For non-medical investigations, MRI and fMRI have largely taken over the research field (Figure 4.31). However, PET is still important, because different tracers can be linked to different molecules. The distribution of neurochemicals in receptors can therefore be determined.

Today, it is not possible to have high spatial and high temporal resolution at the same time using the same recording device. There is a tradeoff. Methods like fMRI and PET tell us *where* in the brain something is happening. EEG, MEG and single cell recordings show millisecond changes in the brain. In any study, it is important to ask why the authors chose a particular method, and what they observed – or might have missed – by the choices they made. In the best cases we can see different methods showing convergent results.

3.1 Regions of interest

Finding your way around the brain is not easy. An even harder task is to figure out which areas play which roles in major cognitive processes such as language, attention and vision. One way is to define regions of interest (ROIs) ahead of the research study, and to make predictions about expected activity in ROIs.

3.1.1 Co-registration of functional activity on a structural scan

The first step is to define the living brain anatomically, to make out different areas, connections and layers of organization. Structural MRI gives us a tool to map out

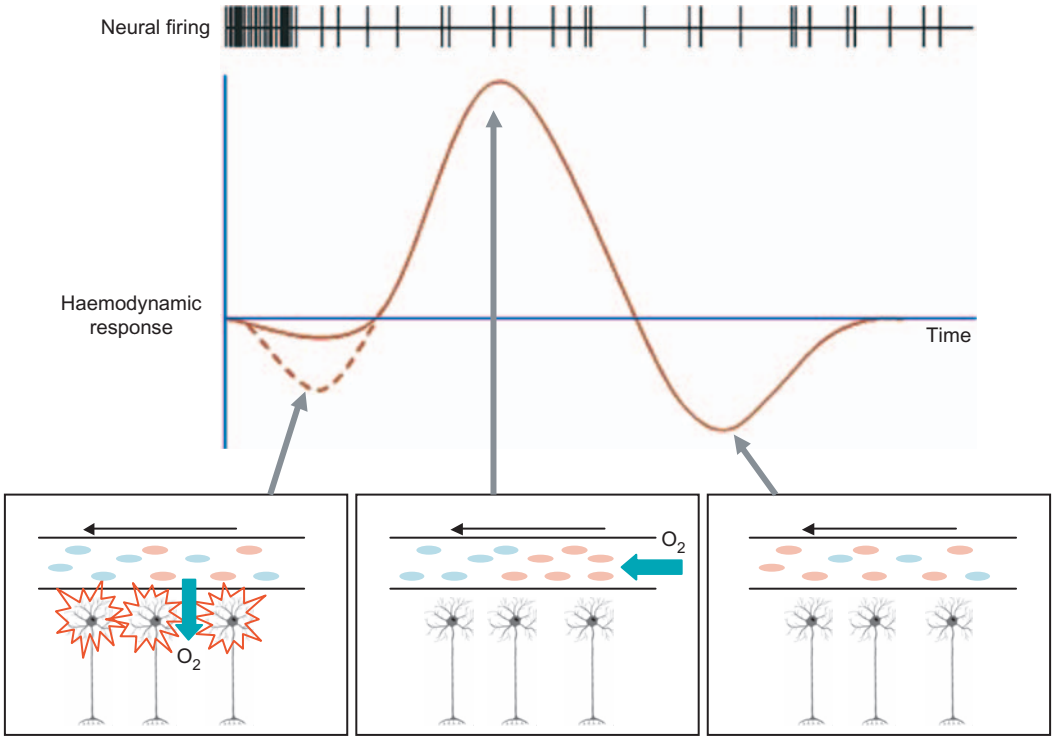


FIGURE 4.29 A typical BOLD response to a neural population. The top line shows a burst of activity in a population of neurons somewhere in the brain. In a few seconds, the active brain region has used up its immediate supply of nutrients – oxygen and glucose. The BOLD curve therefore dips to reflect the loss of oxygen. Next, an upward sweep of the BOLD curve reflects a wave of new, blood-carried nutrients to the active region to keep it going. This wave of oxygen is used up again by energy-thirsty neurons, and the curve dips down again. Eventually, the nutrient supply comes to equilibrium with the neural demand, and the curve goes back to baseline. The BOLD response is called 'hemodynamic' because it reflects fast and precise changes in the local blood supply.

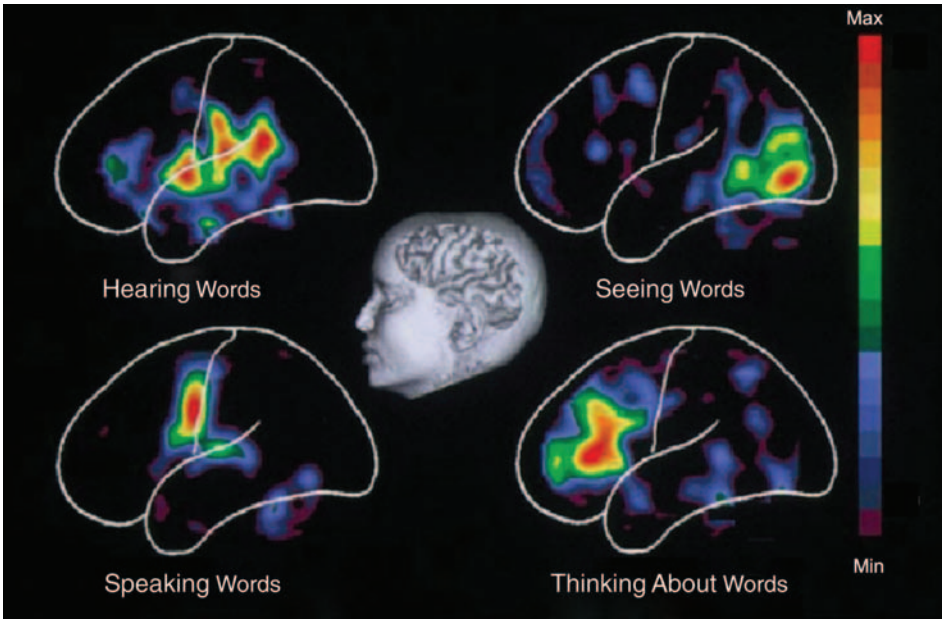


FIGURE 4.30 A classical PET finding: visual versus auditory brain activity. Early PET scans showing different speaking, seeing, hearing, and internally generating words (Posner and Raichle, 1994). Notice that visual, auditory, motoric, and speech production regions appear to be activated. However, the surrounding brain outline (white lines) is only approximate. In more recent brain images, the functional activity would be superimposed upon a structural MRI of the same subject's brain. *Source*: Posner and Raichle, 1994.

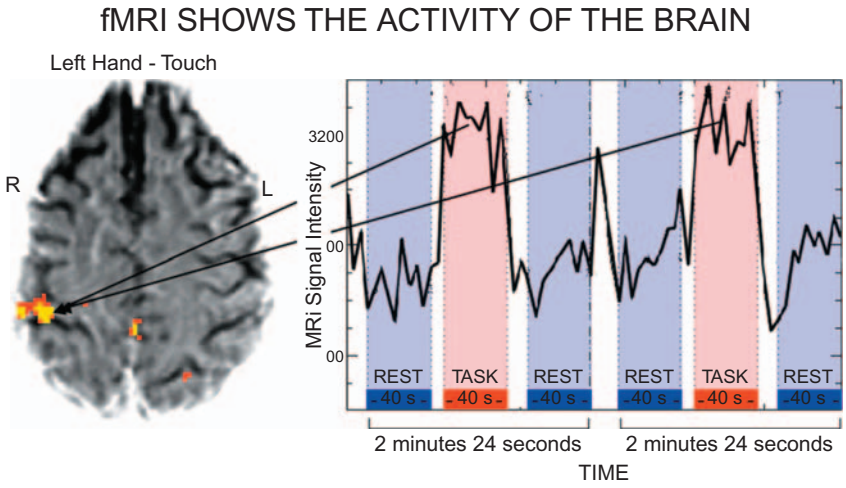


FIGURE 4.31 How the BOLD signal cycles on and off. The basic physics of BOLD requires a high magnetic field to be turned on and off frequently to detect the radio frequency changes due to spin changes in oxygen atoms. Because cognitive tasks occur over seconds and fractions of seconds, a common method is to alternate Task and Rest conditions every half minute or so (in this case, 40 seconds per phase). This allows for excellent within-subject control. On the left, the functional signal (i.e. BOLD) is superimposed on a structural brain scan (using MRI). All brain images superimpose the task-related activity upon brain structure, and average out background activity. *Source*: Robinson, 2004.

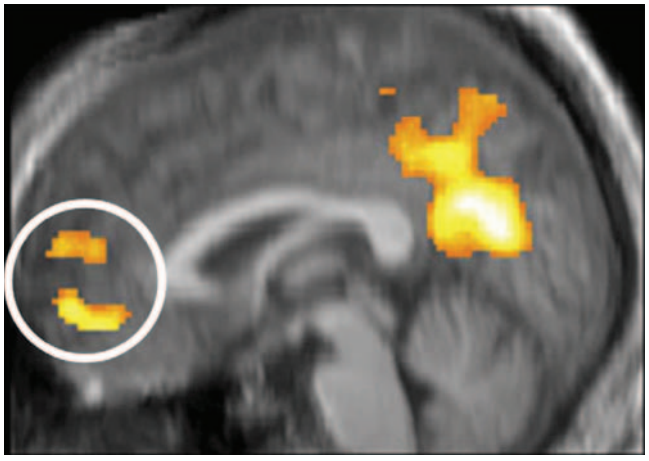


FIGURE 4.32 The BOLD fMRI signal for pain on the left side of the body. By stimulating the left hand to produce mild pain, a BOLD signal emerges in the right-side body map (somatosensory cortex, not shown), and also in these areas along the midline of the right hemisphere. The pain pathways are well known, and mild pain perception is an easy way to test the fidelity of a brain imaging technique. *Source:* Valet *et al.*, 2004.

brain structure, including the axonal (white matter) connections between brain regions. MRI shows structure but not function.

On the right side of Figure 4.32, we see an image with two yellow 'hot spots', reflecting increased fMRI activity. The color is arbitrarily chosen to indicate the degree of activity. In order to pin down the location of the yellow hot spots, we need to superimpose the functional image on the structural MRI, which has a better spatial resolution. In a process called *co-registration*, the functional and structural images are aligned to each other. Co-registration ensures that the two images end up in the same space using the same metric. With higher spatial resolution we can ask questions that are anatomically specific.

Another approach is to mark regions of interest (ROI) on the structural image alone, to constrain the statistical analysis.

Newer MRI machines (Figure 4.27) with higher magnetic field strength now make it possible to look at the cellular organization of the living brain, and to compare brains between groups of people (e.g. people with schizophrenia and healthy subjects). Different layers of cortex have either local or distant connectivity, so that layer information is useful to find out how cortical regions interact.

Because the brain is remarkably active at all times, it is still a challenge to isolate fleeting, task-related activity. One common method is *subtraction* between fMRI conditions: for example, the brain's response to the task of interpreting Arabic numerals (1, 2, 3, . . .) is compared to its response to the same numbers when they are spelled out in printed words (one, two, three, . . .) (Figure 4.33). Subtraction is used because it tends to

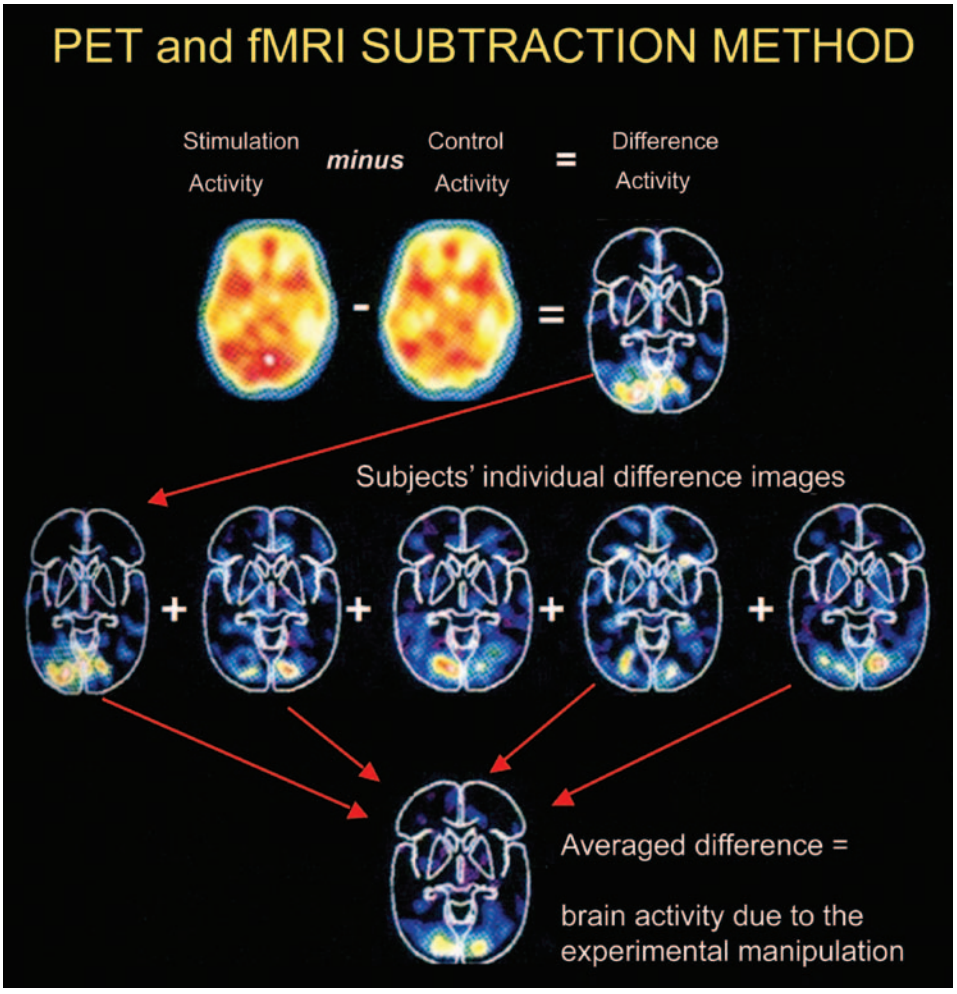


FIGURE 4.33 The subtraction method for PET and fMRI. The brain has constant dynamic background activity. To remove background activity, the BOLD or PET signal for an experimental task is subtracted, point by point, from a closely-matched control task. Individual scans of the differences are then averaged, and produce the group average. *Source:* Posner and Raichle, 1997.

remove most of the 'irrelevant' brain activity, which would otherwise drown out the signal of interest. It is much like comparing a choppy sea before and after a whale swims by. If you want to see the waves generated by the whale alone, you might subtract a record of the waves alone. It is the *difference* between the two conditions that matters (see Figure 4.33).

Subtracting conditions can have unwanted consequences. There might be important things going on in both conditions. In addition, the variance of experimental and comparison conditions might be different, there might be interactions between independent variables, and so on. Another approach therefore is *parametric variation*, in which the variance for each main variable and their interactions, can be separated statistically. For example, if you study working memory (WM), instead of subtracting brain activity during working memory from activity without it, one can study how gradually increasing the WM load leads to changes in neural activation. Since statistical testing must be done for every point of interest in the scan, over every unit of time, this is a large data set.

3.2 The resting brain is not silent: intrinsic brain processes

As neuroimagers began to study different cognitive functions, the main approach was to use a contrastive, subtractive approach. Here, the neural activation during a given cognitive function, such as speech production, was compared to a period where subjects were instructed to relax and 'do nothing'. Such active-versus-rest comparisons showed powerful main effects. Hundreds of comparison studies have been conducted to map the brain regions for cognitive functions.

Yet there is a hidden assumption in these studies. If you are asked just to lie still and 'rest' what will you do? Will your mind be a blank screen? A great deal of evidence shows that people just go back to their everyday thoughts, images, and feelings. You

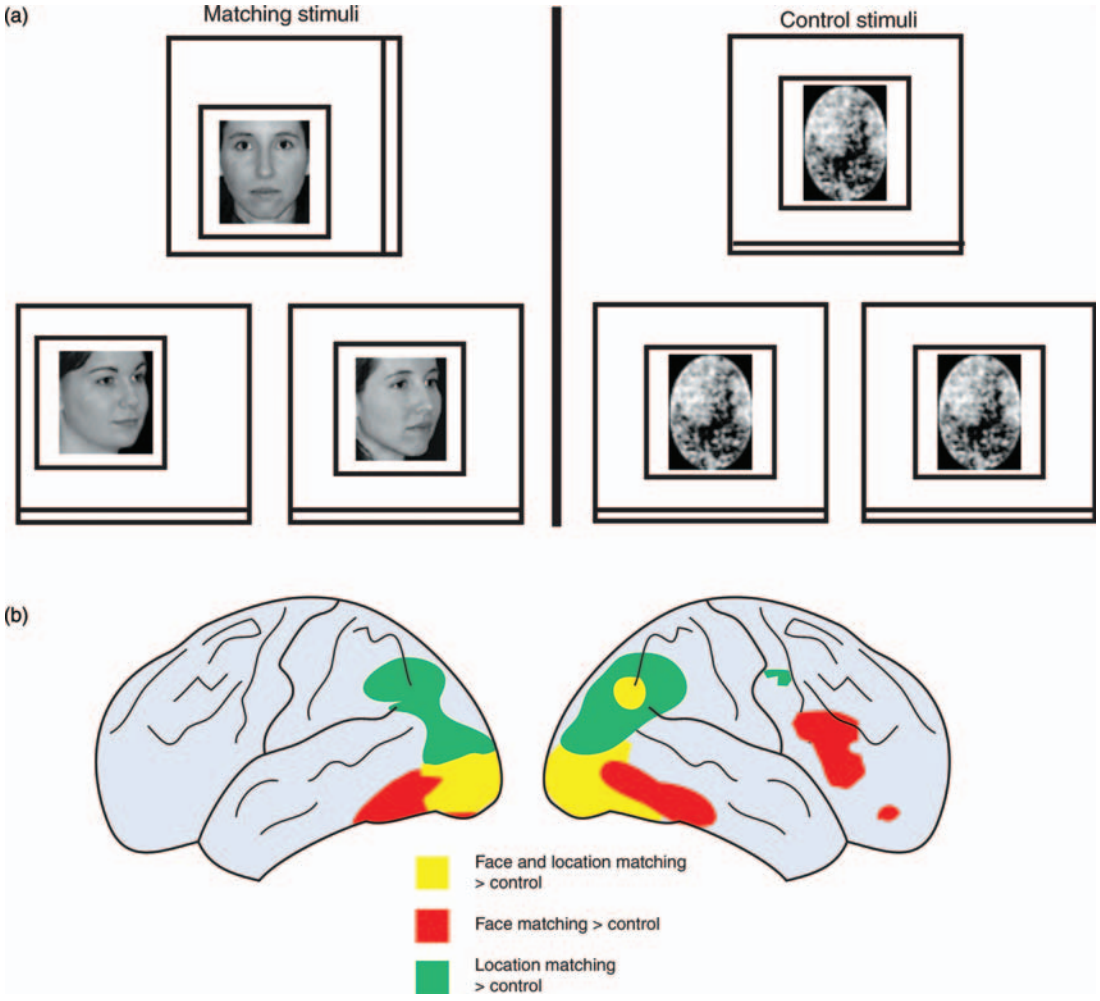


FIGURE 4.34 A typical visual experiment using fMRI. Note that the visual faces are closely matched with visually similar stimuli. The face stimuli are compared to nonface objects in the same spatial orientation. Subjects need to pay attention, so a matching task is used, in which they press a button when the matching stimulus appears. The results show higher BOLD signals for faces in red areas, higher for location in the green areas, and higher face + location in the yellow-shaded parts of the brain. *Source:* Squire *et al*., 2003.

might be thinking about something that happened the day before; or that you need to do later, or even daydream a bit. You are likely to have inner speech, visual imagery, episodic memories coming to mind and so forth. For the brain, that is not 'rest'. Instead, the experimental comparison is really between two active states of the brain. One is driven by experimental task demands, while the other reflects our own thoughts, hopes, feelings, images, inner speech, and the like. In some ways, spontaneous activity may tell us more about the natural conditions of human cognitive activity than specific experimental tasks. Both are obviously important.

An important literature has now sprung up to study the cognitive 'rest' condition, i.e. a condition under which subjects are not asked to do anything in particular (Figure 4.35).

The use of MRI to produce both precise anatomical images and to provide functional maps of brain areas has literally revolutionized the field of cognitive neuroscience. New and better ways to use fMRI are presented in the following section.

3.3 Empirically defining cognitive functions: the creative key

The best science is done by combining imaging techniques with genuine creativity. A lot of creativity goes into the selection of functional variables. What is the best way to understand vision? Selective attention

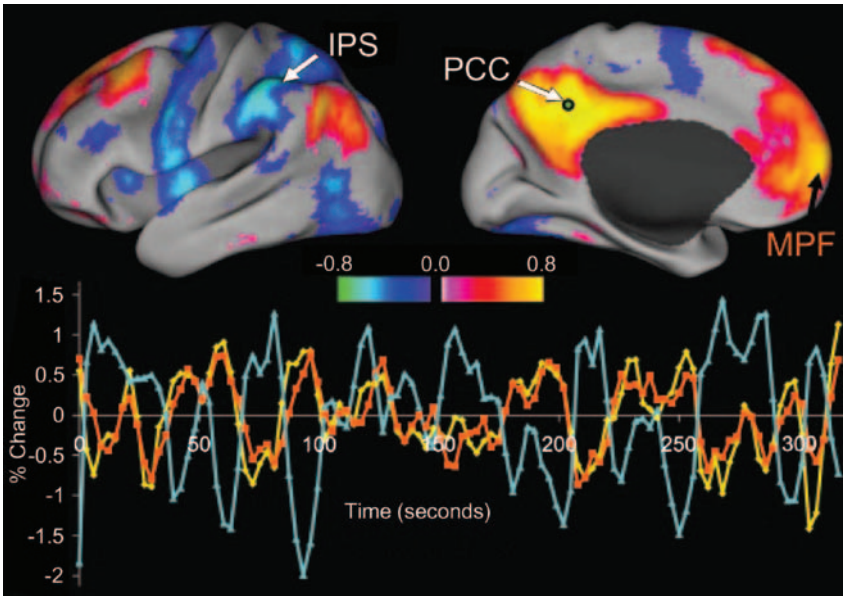


FIGURE 4.35 The brain is an active place. This fMRI shows spontaneous brain activity in both the left hemisphere (left) and the right hemisphere (midline view, right). The bottom shows these activities over 300 seconds. While such 'task-unrelated' activity is different from typical experimental tasks, we know that humans are constantly thinking, imagining, feeling, anticipating, remembering, and talking to themselves, even without being given a specific task to do. *Source:* Fox *et al*., 2005.

and conscious cognition? A great deal of ingenuity has been devoted to those questions.

Here are a few examples. For example, taxi drivers are well known for their ability to know their way around a city. They know not only how to get from A to B, but also the most efficient way to get there. Such ability to navigate through a complex road system depends on our spatial ability. Studies have shown that the hippocampus, a part of the medial temporal lobe, plays an important part in the navigation and memory of places and routes. Rats with lesions to the hippocampus have been known for decades to perform disastrously on spatial tests. Birds and other animals that bury or hide their food at multiple places have larger hippocampi than non-storing animals. Therefore, one question that arises when we think about taxi drivers is, are the brain regions responsible for spatial navigation more developed in taxi drivers than other people? Indeed, it has been found that part of the hippocampi (posterior) of taxi drivers was larger than the same region in a group of people with a different background (see Figure 4.36). OK, you might question, but what if people with large hippocampi choose to be taxi drivers, and not vice versa? Here, the study showed that the size of the hippocampus depended on how long people had been working as taxi drivers. In other words, the longer you work as a taxi driver (and use your spatial navigation ability) the bigger your relevant part of the hippocampus will become.

Notice how imaginative the taxi driver study was. It is usually easier to randomly select human subjects

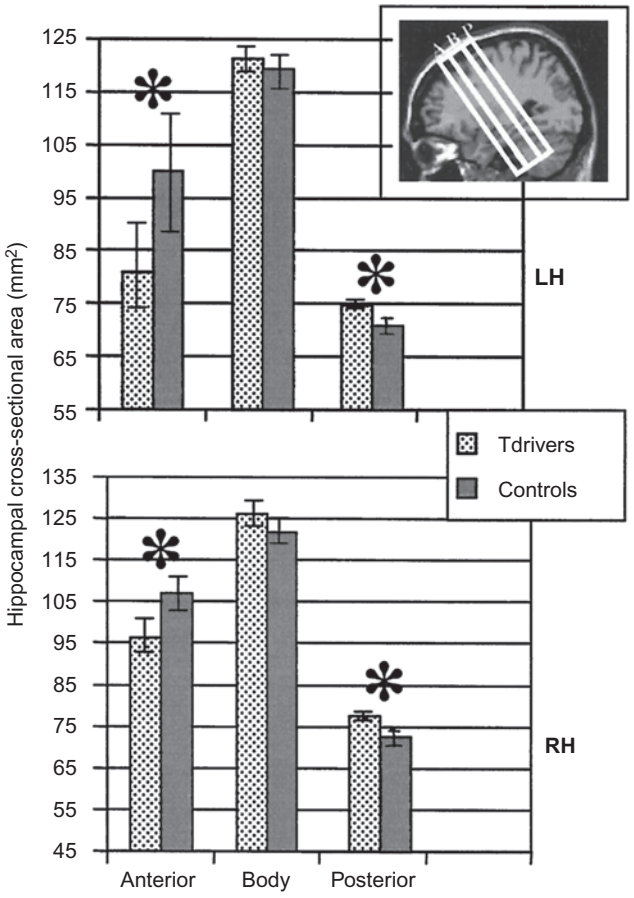


FIGURE 4.36 Hippocampal size in London taxi drivers. London taxi drivers showed substantial differences in the size of a spatial region of the brain, the posterior hippocampus. *Source*: Maguire *et al*., 2000.

(usually undergraduate students!) to stand for the entire human population. But the fact is that there are differences of age, particular abilities and talents, and other cognitive capacities between 'average' subjects. London taxi drivers are highly experienced experts (they are required to pass tests on the geography of the city), and they can be compared to a plausible control group. One important implication is that the sheer size of brain structures may change with specific experiences (Maguire *et al*., 2000). That claim has now been supported for other brain regions as well. The taxi driver study is therefore an excellent example of creative selection of comparison conditions, leading to new insights.

4.0 NEW WAYS TO MEASURE BRAIN CONNECTIVITY: DIFFUSION TENSOR IMAGING

White matter fiber tracts are the vast internal highway system of the cortex. We can visualize these fiber tracts using an MRI method called *diffusion tensor imaging* (DTI). DTI uses water flow in the white matter to measure the relative direction of white matter tracts. This information allows us to investigate connectivity patterns across the two hemispheres and along the four lobes of the brain (see appendix for more details on how this is measured). DTI helps us understand brain connectivity patterns in the healthy brain as well as investigate these patterns in individuals with brain diseases that affect white matter, such as multiple sclerosis (MS).

By far the largest fiber bundle in the brain is the corpus callosum (see Chapter 5), which connects the two hemispheres, but there are many other fiber bundles or tracts that connect regions within the hemispheres. Look at the figure at the beginning of this chapter – it shows a map of colored fibers that spread up from the corpus callosum through cortex. The scientists who prepared this figure color-coded the fibers in the different brain regions, with green fibers in the frontal lobe, moving to yellow in the occipital lobe. Another view of the vast array of white matter tracts is shown in Figure 4.37, with a midsagittal (center-line) view of the fiber tracts that extend upward from the spinal cord to cortex and tracts that extend downward from cortex to the spinal cord. These fiber tracts make up the vertical 'traffic arteries' that flow to and from the cortex and that provide the connective pathways throughout the central nervous system. What is the relationship between fiber tracts and cortical anatomy?

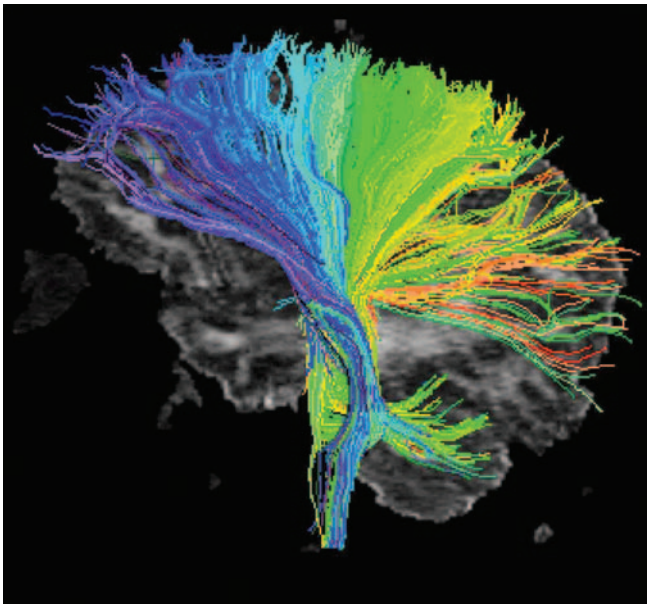


FIGURE 4.37 A fountain-like image of the white fiber tracts. This beautiful spray of neuronal tracts results from a magnetic imaging technique called diffusion tractography, which allows us to view the white (myelinated) fiber tracts. These are the vertical traffic arteries that flow from the cortex (especially frontal ones, in blue) down into the spinal cord; and upward from the spinal cord to the rear half of cortex (in yellow and green). Most of the volume of cortex is taken up by these massive fiber tracts. *Source*: Maria Lazar, with permission.

A recent study investigated the correspondence between white matter and gray matter and results are presented in Figure 4.38. Constructed maps of peripheral white matter tracts are presented at the top of the figure and their corresponding cortical gray matter regions are shown below. Note that Figure 4.38 shows the same information across three views of the brain: from the front or anterior perspective (A and D), from the same or lateral perspective (B and E), and from the back or posterior perspective (C and F).

5.0 CONSCIOUS VERSUS UNCONSCIOUS BRAIN EVENTS

Conscious cognition is a new direction in cognitive neuroscience. It involves trying to understand the difference between conscious and unconscious brain events. In the last decade or two, scientists have made use of many experimental paradigms to compare the two. One major example is binocular rivalry, presenting a stream of two different visual stimuli to the two eyes, so that only one stream of input is conscious at any given time. Behaviorally, humans can only report one stream

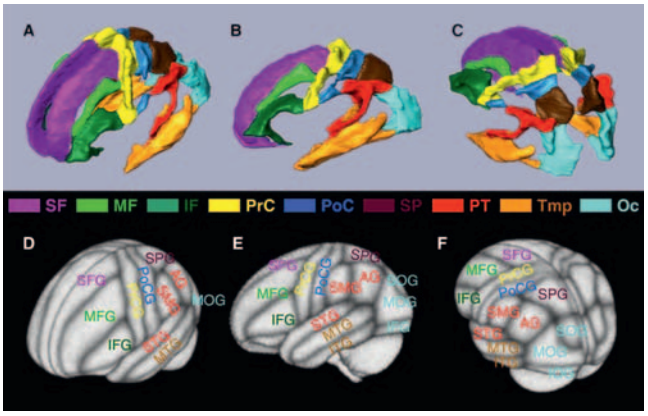


FIGURE 4.38 Diffusion tractography brings out the corpus callosum and other large fiber tracts. Notice that we are looking at a cutaway image of the brain, in which the right hemisphere is intact. We can see the green-marked fibers projecting upward in front, and yellow-marked ones projecting toward the rear. Different artificial colors are assigned by computer to different directions of travel of the fiber highways. The c-shaped or banana-shaped structures in section (b) are the corpus callosum (the 'calloused body'), which looks white to the naked eye. The corpus callosum contains about 100 million fibers, running sideways from one hemisphere to the other. Millions of cells in the left hemisphere connect to a corresponding point in the right hemisphere. *Source*: Huang *et al.*, 2005.

(see Chapter 6). Binocular rivalry works in macaque monkeys much the way it does in humans (Logothetis, 1998), and the wave of current interest in visual consciousness may be dated to a classic series of binocular rivalry studies in macaques, using single neuron recording at different levels of the visual hierarchy (Sheinberg and Logothetis, 1997); see also the discussion of binocular vivalry in Chapter 6.

6.0 CORRELATION AND CAUSATION

We typically combine brain and behavioral observations. We can present visual images on a screen and have the subject read aloud or meditate. Thus, we typically observe a *correlation* between behavior and brain activity. In methods with high spatial resolution, such as fMRI, different tasks show local increases or decreases in the BOLD signal, indicating that the brain works more in some regions than others (see Figure 4.31).

We can take the example of the 'Counting Stroop Task', in which subjects are asked simply to count the number of words shown on a computer screen. On some occasions a word like 'dog' is shown three times. The subject should say 'three', which is not difficult. However, we can introduce a conflict between the words shown and the number of words. If we show the word 'one' four times, there is an automatic tendency for expert

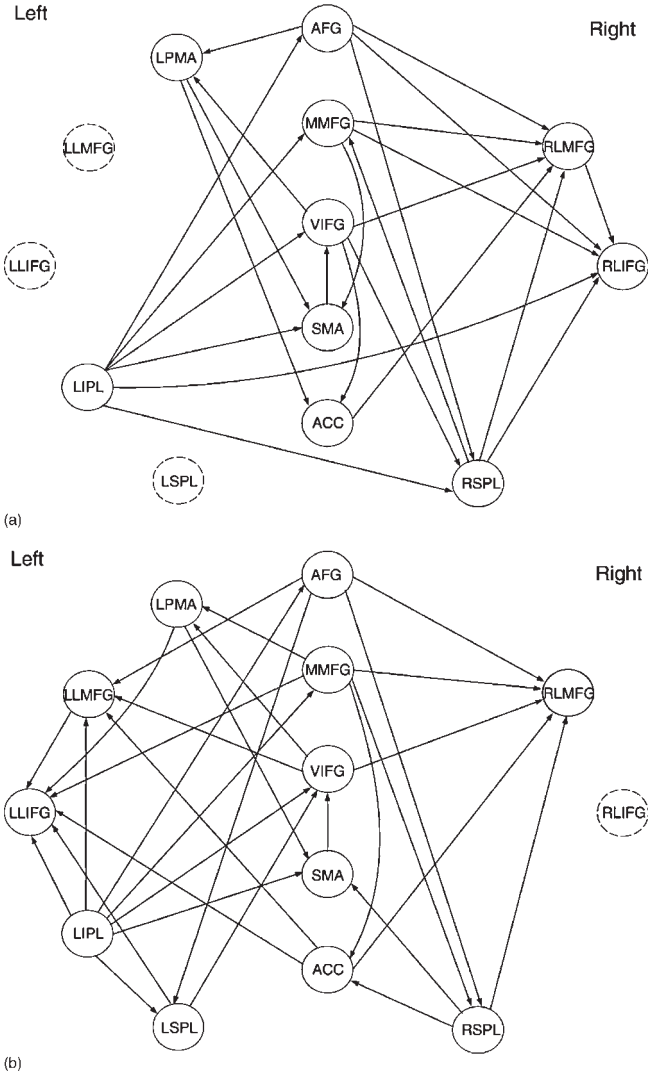


FIGURE 4.39 Causal relationships between brain activities during the Stroop task. Brain activity during simple counting with no interference is shown at the top (a), and the activation during counting with interference is shown at the bottom (b). Each circle represents a region of the brain. As can be seen, interference (b) leads to the engagement of a more widespread network than the control condition (a). This change in causal coupling between brain areas is seen in spite of the fact that many of the same areas are active in both conditions. Note also that some of the connections are lost between the control and the interference condition. (Adapted from Zheng and Rajapakse, 2006.)

readers (like college students) to say the word 'one'. But the correct answer is 'four'. This is very much like the Color-naming Stroop Task (see Chapter 2). Subjects take longer to answer correctly, since they must inhibit their automatic tendency just to read the words on the screen.

Zheng and Rajapakse (2006) reported the BOLD activity during the two versions of word counting (Figure 4.39). While many brain regions show activation during both conditions, frontal parts of the brain were more active

during the conflict condition. This kind of result has now been found many times for conflictual tasks. One of the major roles of prefrontal cortex is to resolve conflicting tendencies, like the automatic tendency just to read words, against the tendency to follow the experimental instructions. Thus, we have a correlation between (a) frontal activation, (b) longer reaction times, (c) a sense of subjective effort, (d) a greater number of errors in the conflict condition. These are significant results, since there are many real-life conditions where conflicting tendencies need to be regulated.

However, so far we have no way to test *causal* hypotheses. For example, we know that the task requires visual word recognition, response preparation, choosing between two possible answers, perhaps detecting conflict, stopping the wrong answer from being said, selecting the right answer instead, and so on. An approach called *dynamic causal modeling* (DCM) is one to analyze for causal relationships. Zheng and Rajapakse (2006) performed DCM on the brain activation they found in both word counting tasks. As you can see in Figure 4.39, DCM suggested that each task had a different activation pattern. Although many of the same regions of the brain are active during both tasks, their relative connectivity and contribution was altered. Interestingly, the analysis also showed that the interference condition recruits wider activity than the control condition. This is another common finding for mentally effortful conditions (Duncan and Owen, 2000).

6.1 Why we need multiple tests of brain function

According to some media headlines, brain scientists recently discovered the parts of the brain used for deception and lying. This kind of headline comes from studies like the one shown in Figure 4.40. It shows fMRI differences between brain regions that had greater BOLD activity when people were telling the truth (green) and cortical areas when they were made to tell a lie. Such experiments often use playing cards, and ask a group of subjects to 'lie' by reporting a different card than the one they actually see.

One major purpose of cognitive neuroscience is to identify function with structure, i.e. to see whether specific brain locations do specific things for us. In that process, however, we must be very clear about the kinds of inferences that we can make from the evidence. The popular media may not be quite as careful as scientists need to be. Do you believe that the green areas in Figure 4.40 are really the 'truth telling' areas of the brain?

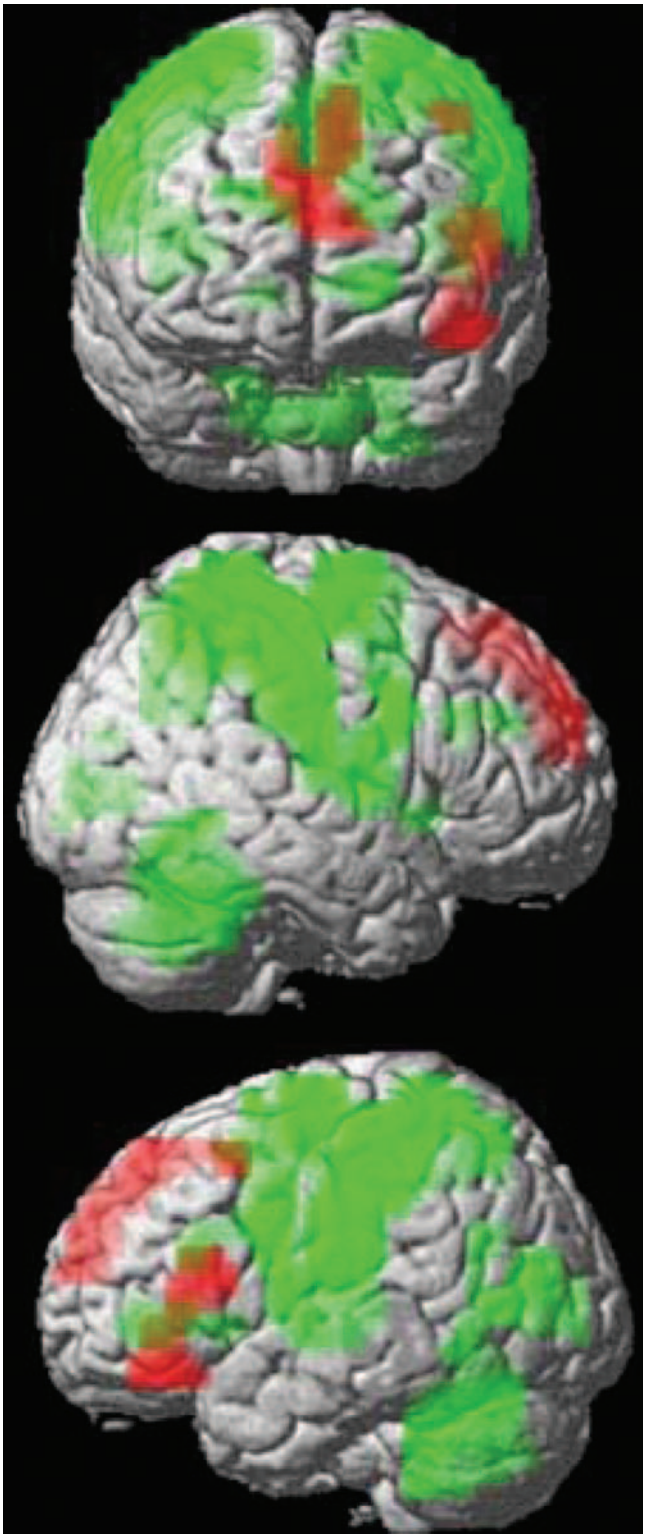


FIGURE 4.40 Are these the truthful and the deceptive areas of the cortex? fMRI differences between brain regions that had greater BOLD activity when people were telling the truth (green) and cortical areas when they were made to tell a lie (red). Is this the truth-telling cortex (green) and the lying cortex (red)? Why or why not? *Source*: Davatzikos *et al*., 2005.

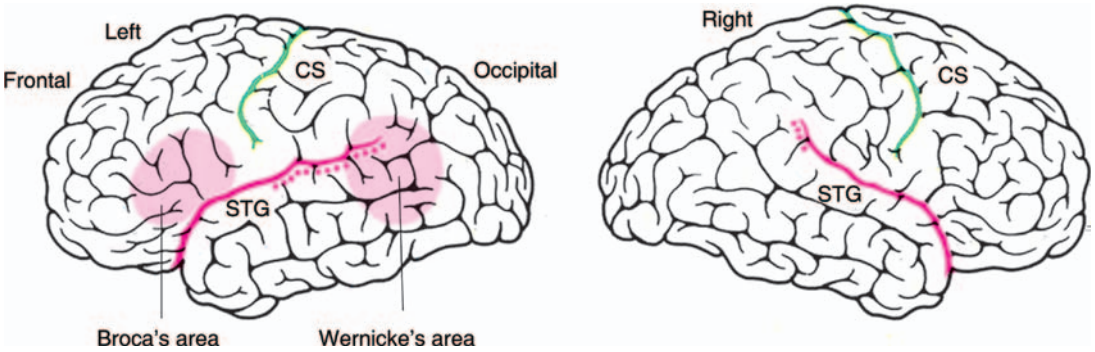


FIGURE 4.41 Language area lesions. Lesions to either Broca's or Wernicke's areas produce very different effects on language. Notice that the right hemisphere has no Broca's and Wernicke's areas, traditionally, even though it is involved in the comprehension of speech and language. *Source*: Standring *et al*., 2005.

6.2 Brain damage and causal inferences

Brain injuries can provide evidence areas that are necessary for certain cognitive functions. Historically, Paul Broca discovered patients who were unable to speak and also showed damage to the left frontal lobe. However, their ability to comprehend language was relatively spared. About the same time, Carl Wernicke made the discovery that damage to different regions of the left hemisphere was associated with the ability to understand language, while their ability to speak was intact. Today, we call this complementary pair of facts a *double dissociation*.

Brain damage is correlational, since we cannot produce it and test its results in humans. Nevertheless, after a great deal of debate and controversy, there is no serious doubt today that one important function of Broca's area is the production of speech, and likewise, that one important function for Wernicke's region is speech comprehension (Figure 4.41). Lesions near Broca's area can lead to *dysarthria*, a condition where the control of mouth and tongue movement is disrupted, but language production is still intact. Thus, we have three lesions that lead to three different speech problems: one seems to be important for language comprehension; another is vital for language production; and a third region is important for the motor commands to produce vocal expressions.

Brain injuries in humans happen for a host of reasons, ranging from car accidents to strokes. Accidental lesions do not neatly follow the borders between brain regions. To test brain-mind hypotheses it is preferable to be much more precise about exactly where in the brain deficits occur. In order to do this, studies have been conducted in experimental animals, typically rats and monkeys. However, language is a species-specific function for humans, and we have no direct parallels in other species. (However, as mentioned above, there is now a way to produce safe interference in specific brain areas, using TMS.)

Very precise lesions have been studied in monkeys and rats for many years, with significant results. For example, Buckley and Gaffan (2006) made precise lesions in different areas of the medial temporal lobe (MTL) in macaque monkeys. Very specific damage to the *perirhinal* cortex (meaning 'near the smell cortex') caused monkeys to make more errors on a visual object discrimination task. Lesions to surrounding areas did not produce this deficit. The harder the discrimination task became – the more alike the visual objects were – the more errors were made by the lesioned monkeys. Yet the monkeys performed normally in simple visual discriminations between different colors, shapes and orientations. This suggests that the perirhinal cortex may have a specific *causal* role in processing complex visual objects like faces. A variety of human studies now support this finding. Animal studies have often played this pioneering role, allowing us to pick up leads that are later tested and often verified in humans.

Comparing damaged and healthy brains is a powerful source of evidence for understanding basic neural processes.

7.0 SUMMARY

Brain techniques measure single neurons to large cortical regions, brain structure, dynamic brain activity, and connectivity. The advent of brain imaging has transformed the study of human cognition. New and more refined methods are constantly being produced. One recent advance is to use multiple methods in the same study, so as to optimize the tradeoffs between electromagnetic and indirect measures of brain activity.

8.0 CHAPTER REVIEW

8.1 Drawing exercises and study questions

1 Label the differences between the brain scans in Figure 4.42, and describe the reasoning of the subtraction method for each image.
2 Define the BOLD response. What does the abbreviation BOLD mean?
3 What is the time lag between neural activity and a BOLD response? Between neural activity and an EEG response?
4 What are the pros and cons of single-cell recording in the brain?
5 What problem might arise when brain activity in a cognitive task is compared to a resting baseline?
6 What does Figure 4.40 tell us about lying and the cortex?
7 Judging by diffusion tractography, how much tissue is devoted to connections between cortical neurons (approximately)?
8 Describe four common brain electrical rhythms. What functions are they often associated with (see Table 4.1)?

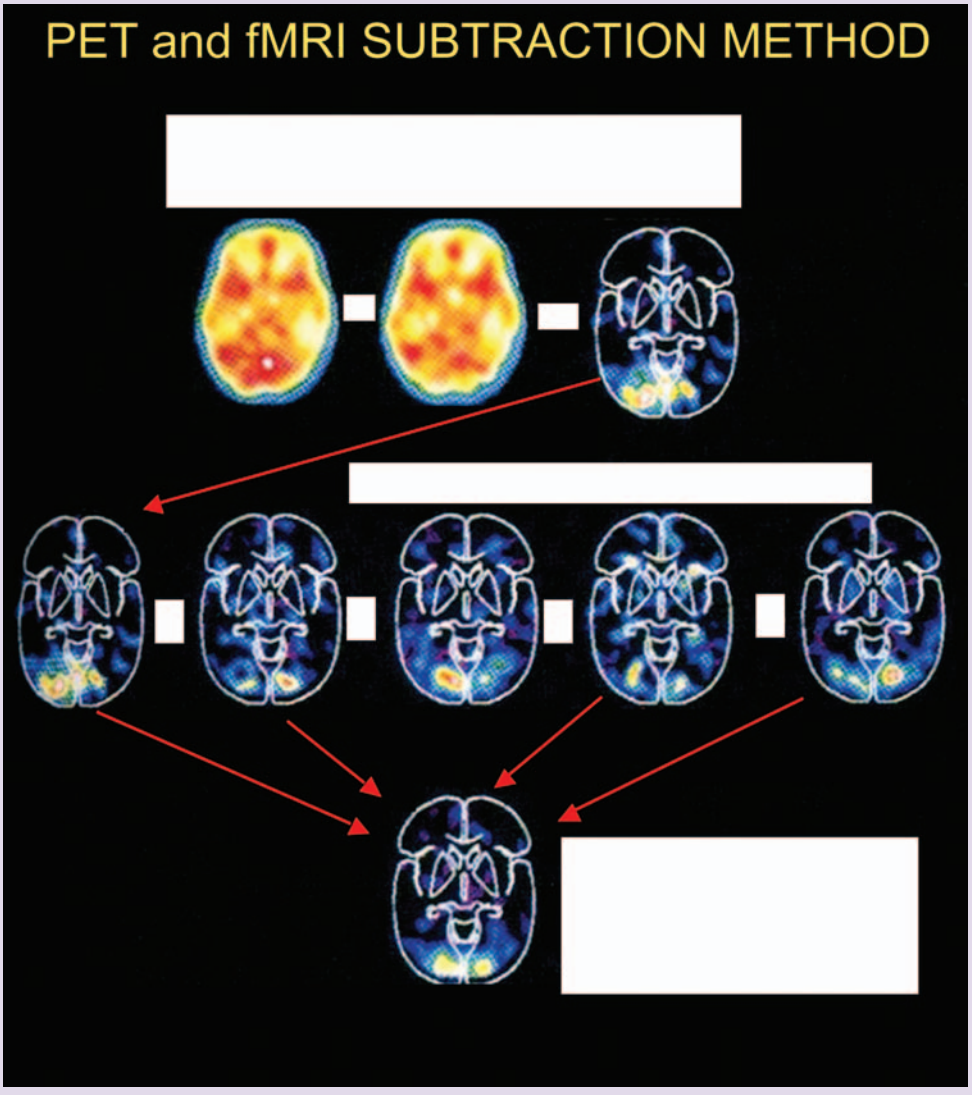
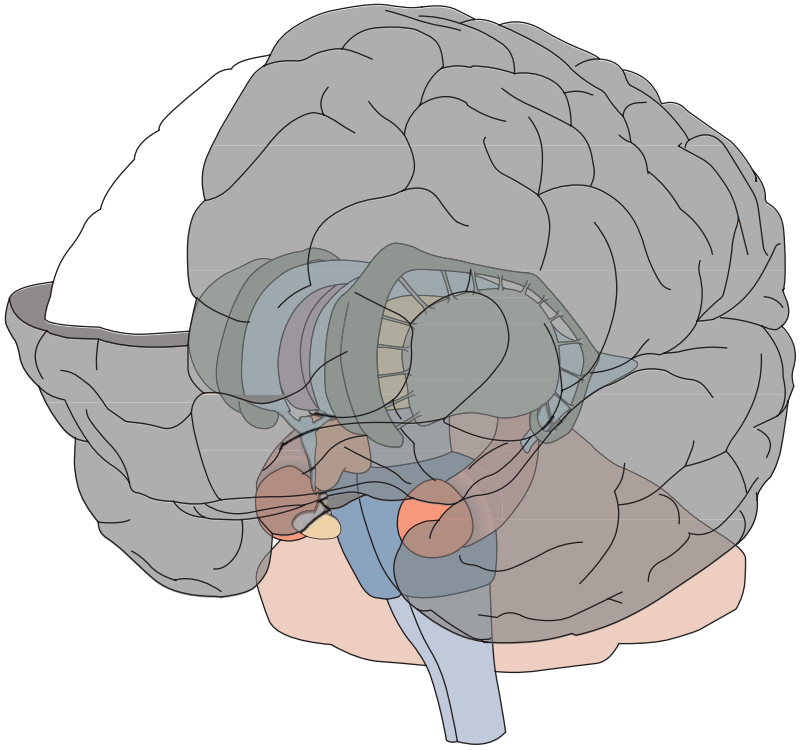


FIGURE 4.42 A reproduction of Figure 4.33 shown without labels for use in the Drawing Exercises.

The brain is contained within the cranium, and constitutes the upper, greatly expanded part of the central nervous system.

Henry Gray (1918)



Looking through the gray outer layer of the cortex, you can see a mass of white matter. At the center is a cluster of large nuclei, including the basal ganglia, the hippocampi, the amygdalae, and two egg-shaped structures at the very center, barely visible in this figure, the thalami. The thalami rest on the lower brainstem (dark and light blue). You can also see the pituitary gland in front (beige), and the cerebellum at the rear of the brain (pink). In this chapter we will take these structures apart and re-build them from the bottom up.

CHAPTER

5

The brain

OUTLINE

1.0 INTRODUCTION

Our brains give us our biggest evolutionary edge. Other large mammals have bigger muscles and greater speed, but humans have an exceptionally big and flexible brain, specialized for excellent vision and hearing, language and social relationships, and for manual control and flexible executive control. Human brains make culture and technology possible.

In this chapter, we look at the structure of the brain, while in the coming chapters we will cover its functions – how it is believed to work. It is important to understand that brain anatomy is not a static and settled field: new and important facts are constantly being discovered. On the microscopic and nanoscopic levels, whole new classes of neurons, synapses, connection patterns, and transmitter molecules have been found. While knowledge of the brain is constantly expanding, we will focus on the basics.

Cognitive neuroscience inevitably focuses on the cortex, often considered to involve the 'highest level' of processing. The cortex is only the outer and visible portion of an enormous brain, one that has developed over hundreds of millions of years of evolution. The word 'cortex' means *bark*, since that was how it appeared to early anatomists. While the cortex is vital for cognitive functions, it interacts constantly with major 'satellite' organs, notably the thalamus, basal ganglia, cerebellum, hippocampus, and limbic regions, among others. The closest connections are between the cortex and thalamus, which is often called the *thalamo-cortical system* for that reason. In this core system of the brain, signal traffic can flow flexibly back and forth, like air traffic across the earth.

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

The major lobes of cortex are comparable to the earth's continents, each with its population centers, natural resources, and trade relations with other regions. While cortical regions are often specialized, they are also densely integrated with other regions, using web-like connections that spread throughout the cortex and its associated organs. This outer sheet is called the *gray matter* from the way it looks to the naked eye. It is the outer 'skin' of the *white matter* of cortex which appears to fill the large cortical hemispheres, like the flesh of a fruit. However, this is only appearance. In fact, the gray matter contains the cell bodies of tens of billions of neurons that send even larger numbers of axons in all directions, covered by supportive myelin cells that are filled with white lipid molecules. These white myelin sheaths of cortical neurons are so pervasive that they make the connections between cortical neurons look white to the naked eye.

1.1 The nervous system

The brain is part of the nervous system which pervades the human body. The two main parts are the central nervous system (CNS), which includes the brain and the spinal cord, and the peripheral nervous system (PNS), which contains the autonomic and peripheral sensory and motor system (Figure 5.1).

Together the CNS and PNS provide a dynamic and massive communication system throughout all parts of the body, with a hub at the brain that is accessed through the spinal cord. We will focus in this chapter on one part of the CNS, the brain (Figure 5.2).

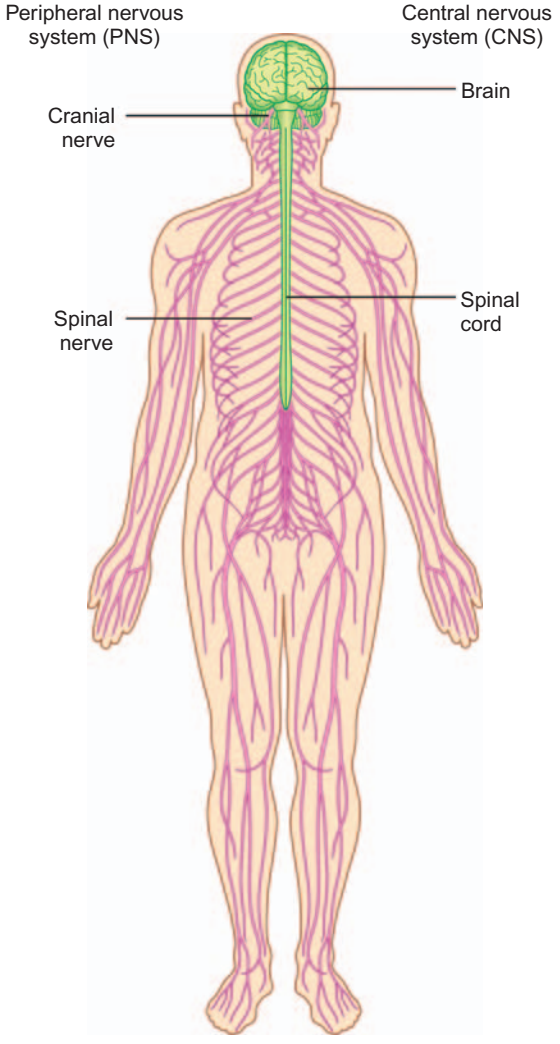


FIGURE 5.1 The central and peripheral nervous systems. *Source*: Standring, 2005.

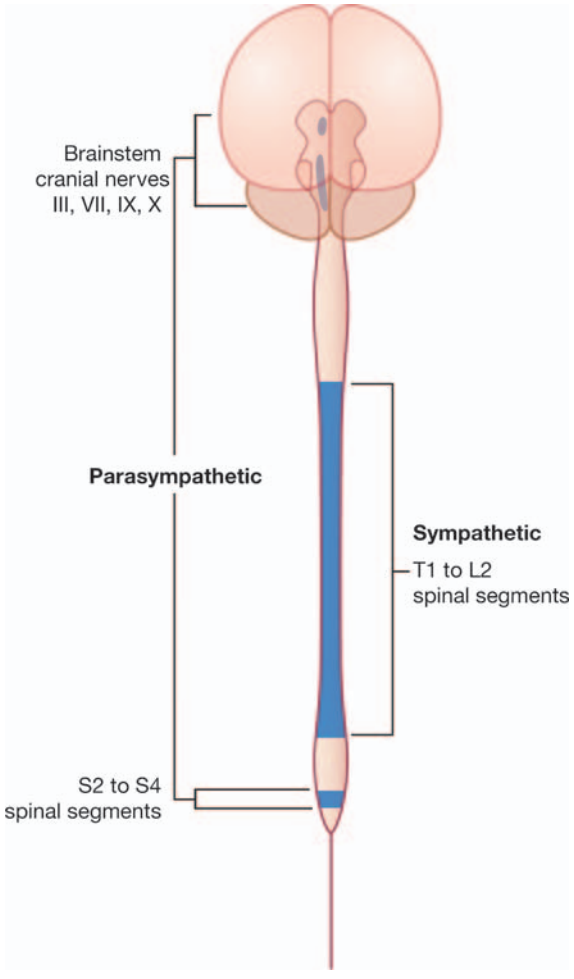


FIGURE 5.2 Parts of the central nervous system include the spinal cord and the brain. *Source*: Standring, 2005.

In this chapter, we will focus on two sensory input systems within the brain: vision and hearing. Although there are other sensory input systems, such as olfaction (smell) and somatosensory (touch), vision and hearing have been most studied in the human brain. We will focus on two output systems, speech and hand-arm control, again because they have been the target of much study. Throughout this chapter on the brain, we will describe the anatomy of the brain and brain regions and we will also highlight the function they serve. We will begin with discussing the many levels of analysis that we can take in describing the brain – from large-scale regions such as cerebral hemispheres and cortical lobes, to finer-scale classifications, such as cortical layer topography.

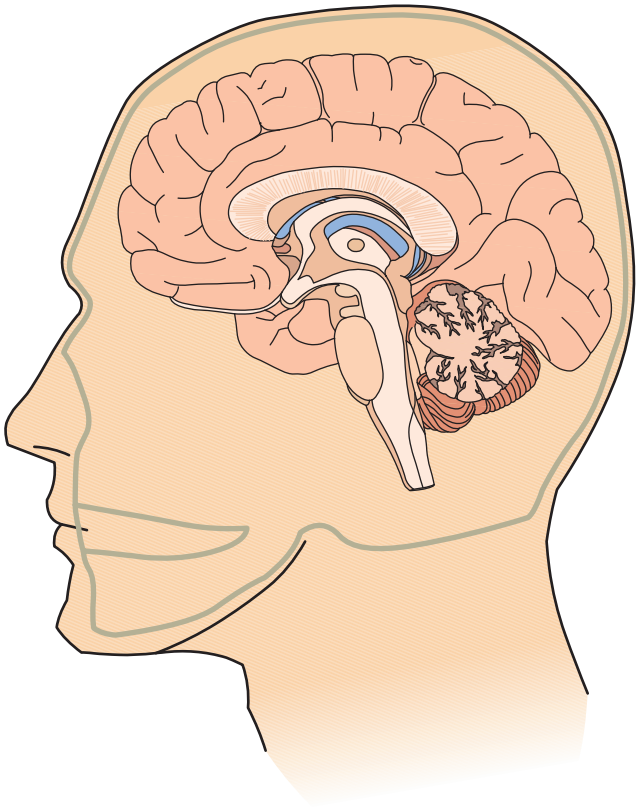


FIGURE 5.3 The location of the brain in the head, showing a midsagittal view of the right hemisphere.

1.2 The geography of the brain

Let's begin with the large-scale brain areas and work our way down to a finer analysis. First, to state the rather obvious, the brain is located in the human head, as depicted in Figure 5.3.

We can look at the brain at different geographical levels – from continents to countries, states, and cities. Thus, we have several levels of detail. The first distinct geographical regions are the two cerebral hemispheres, which are entirely separate, joined through a complex connective region called the corpus callosum. We will discuss the hemispheres in more detail later in the chapter: the question of why we have two separate hemispheres in the brain has long intrigued scientists and philosophers alike.

Next, we have the cortical lobes (Figure 5.4): there are four lobes in each hemisphere. Beginning at the

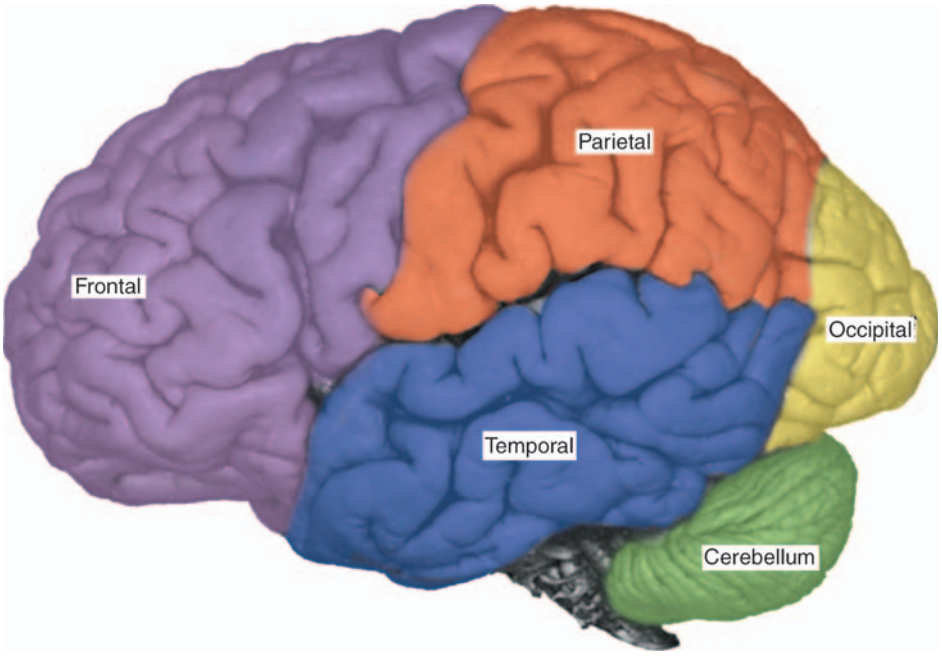


FIGURE 5.4 The four major lobes of the cortex are visible from a lateral view of the brain. Here we show a view of the left hemisphere with the frontal lobe (purple) at the anterior of the brain, the parietal lobe (orange) posterior to the frontal lobe at the superior aspect of the brain, the temporal lobe (blue) posterior to the frontal lobe and inferior to the parietal lobe, and the occipital lobe (yellow) posterior to both the parietal and temporal lobes. Just below the occipital lobe is the cerebellum (green), which is not part of the cortex but is visible from most aspects of the brain. *Source*: Squire *et al*., 2003.

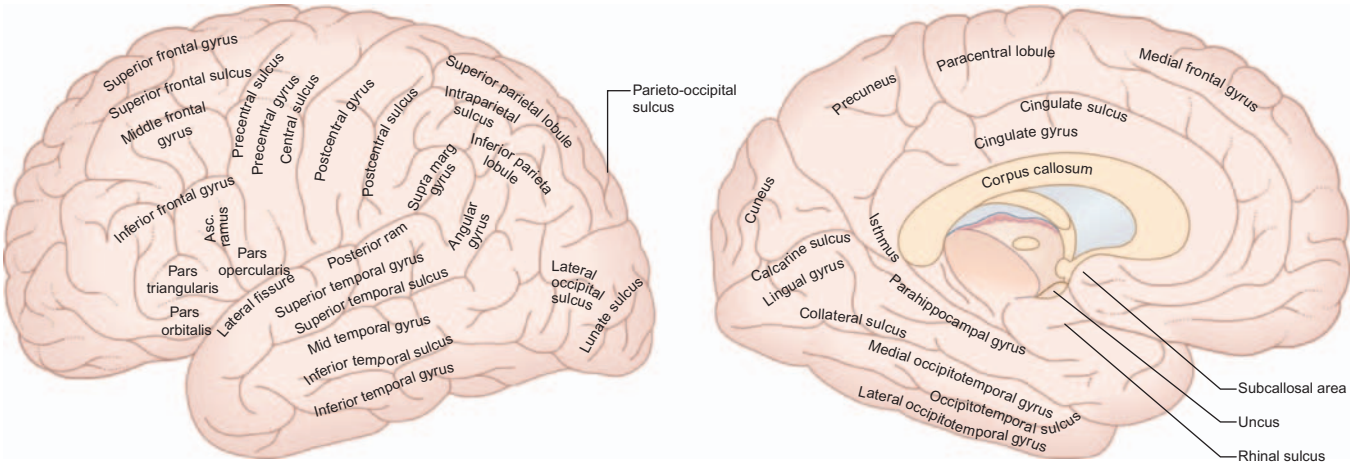


FIGURE 5.5 Some important landmarks of the brain in the left hemisphere from a lateral perspective (left panel) and a midsagittal perspective (right panel). *Source*: Standring, 2005.

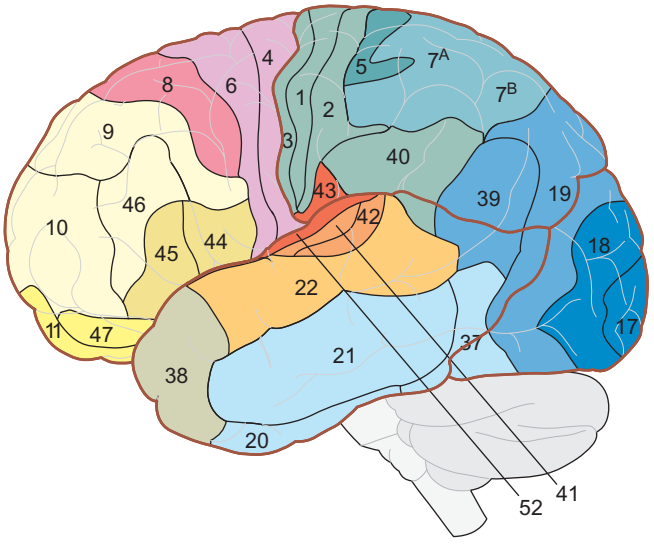


FIGURE 5.6 The Brodmann classification of regions in the left hemisphere, shown in a lateral view. Areas 41 and 52 are indicated by lines. Some areas, like the insula and auditory region, are tucked away behind the temporal lobe.

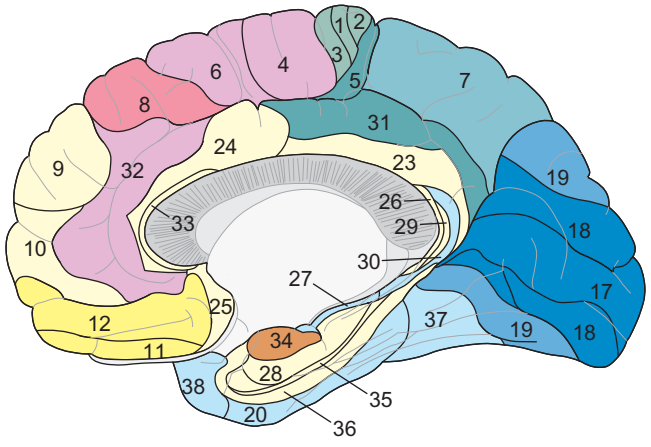


FIGURE 5.7 The Brodmann classification of regions in the right hemisphere, shown in a midsagittal view.

front or anterior part of the brain (shown on the left side of Figure 5.4), we see the *frontal lobe*. Immediately behind the frontal lobe, at the top or superior part of the brain, we find the *parietal lobe*. Below, or inferior to, the parietal lobe and adjacent to the frontal lobe, we find the *temporal lobe*. At the back or posterior part of the brain, we find the *occipital lobe*. We will discuss the anatomical features and cognitive function of these lobes later in the chapter.

We can see the major lobes with the naked eye, along with their hills and valleys, the gyri and sulci. Some of these are so important that we will call them landmarks – we need to know them to understand everything else. In Figure 5.5, we show some of the major landmarks that brain scientists have long used to identify regions in the brain. These landmarks are widely used today when discussing the results of neuroimaging studies.

At a more microscopic level of description, we have the *Brodmann areas*, the numbered *postal codes* of the cortex. When the surface layers of cortex are carefully studied under a microscope, small regional differences can be seen in the appearance of cells in the layers and

their connections. Those subtle differences were first described by Korbinian Brodmann in 1909, and are therefore known as Brodmann areas, each with its own unique number (Figure 5.6 shows a lateral view of Brodmann areas in the left hemisphere, and Figure 5.7 a medial (midsagittal) view of the Brodmann areas in the right hemisphere). About 100 Brodmann areas are now recognized, and it is therefore convenient to take this as a rough estimate of the number of specialized regions of the cortex. The Brodmann areas correspond well to different specialized functions of the cortex, such as the visual and auditory areas, motor cortex, and areas involved in language and cognition. They are essentially the postal codes of the brain. They range in size from a few square inches – the primary visual cortex, for example, is about the size of a credit card – to the small patch of Brodmann area 5 at the top of the somatosensory cortex.

Notice that in Figure 5.6, with the brain facing left, neighboring Brodmann areas are colored to show their major functions including vision, hearing, olfaction, motor control, Broca's area (speech output), and Wernicke's area (speech perception and comprehension). This figure will be used as a reference map throughout this book.

We can focus even more specifically by observing hypercolumns, columns, and single neurons. At this fine level of resolution the current standard is the *Talairach coordinates* (Talairach and Tournoux, 1988), which is used in functional brain imaging. The Talairach system can be compared to the map coordinates of the world, as shown on a GPS locator. They indicate the street addresses of the brain.

It helps here to refer back to Figure 4.3, p. 99. The fine red lines show the axes of a three-dimensional coordinate system. On the upper left, we see the medial view of the right hemisphere, looking to the left (see the small head inset for orientation). In this image, the horizontal red line always runs between the pineal body (not visible), and the small cross-section of the *anterior commissure* – one of the tiny white fiber bridges that run between the two sides of the brain. The three-dimensional zero point (0, 0, 0) of the coordinate system is always at the front of these two points. This allows all three dimensions to be defined with good reliability. Notice the three standard perspectives on the brain: the medial view (midsagittal), the horizontal or axial, and the coronal (crown-shaped) cross-slice. This software display allows any point in the brain to be specified precisely, by entering numbers for the points in three dimensions. While human brains vary a great deal, much as human faces do, the Talairach system allows different brains to be mathematically 'squeezed into a shoebox', so that different brains can be compared in a single framework.

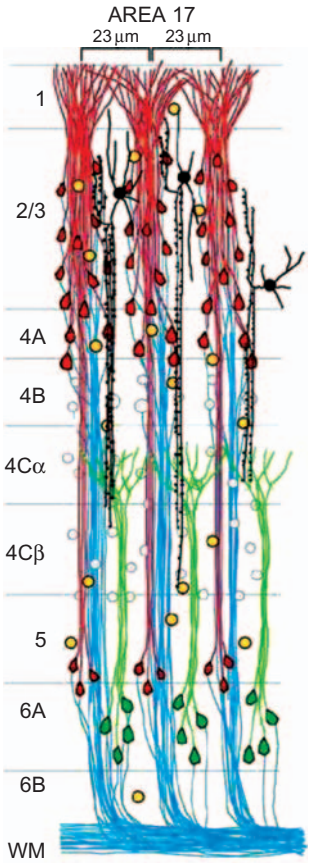


FIGURE 5.8 The six major layers of cortex in cross section. The figure shows three columns in Area 17, also called V1, the first visual projection area to the cortex. *Source*: Squire *et al*., 2003.

Let's continue our description of the geography of the brain with a look at the fine structure of the cortex. The visible outer brain consists of a large thin sheet only six cellular layers thick (Figure 5.8), called the cortex (meaning 'bark', like the outside bark of a tree). This sheet is called the gray matter from the way it looks to the naked eye. Not all cortex has six layers; only the giant mammalian cortex does, and is therefore sometimes called 'neocortex' (That is, the new cortex, because it only emerged 200 million years ago!) Older regions of cortex are also found in reptiles, like salamanders, for example, such as the limbic cortex, which we will discuss later in this chapter. That region has five cortical layers and is sometimes referred to as 'paleocortex'.

The six horizontal layers of cortex are organized in *cortical columns*, vertical barrel-shaped slices (Figure 5.8). These often contain closely related neurons, such as visual cells that respond to different orientations of a single light edge in just one part of the visual field. Columns may be clustered into *hypercolumns*, which may be part of an even larger cluster. Thus, cortex has both a horizontal organization into six layers, and a vertical one, into columns, hypercolumns, and eventually entire specialized regions. The visual cortex of the macaque monkey is often used as an animal model to study vision. Human visual cortex looks quite similar. Note that there are six layers, with numbering (in Roman numerals) beginning at the top with layer I and progressing down to layer VI (Figure 5.9).

The geography analogy is useful, but the brain, like the world, is a dynamic place. New streets are built and old ones move or are rebuilt. Houses and their residents appear and disappear. Until about a decade ago, it was believed that neurons did not change in the adult brain, but we now know of a number of ways in which neurons continue to grow, migrate, connect, disconnect, and die, even in the healthy mature brain. The brain is never frozen into a static rock-like state.

These dynamic aspects of the brain can be seen even at the level of the six layers of cortex. Let's take another look at the six layers of the cortex, this time using a schematic drawing of the layers and their inputs and outputs (Figure 5.9). Notice that some cortical neurons send their axons to the thalamus, while

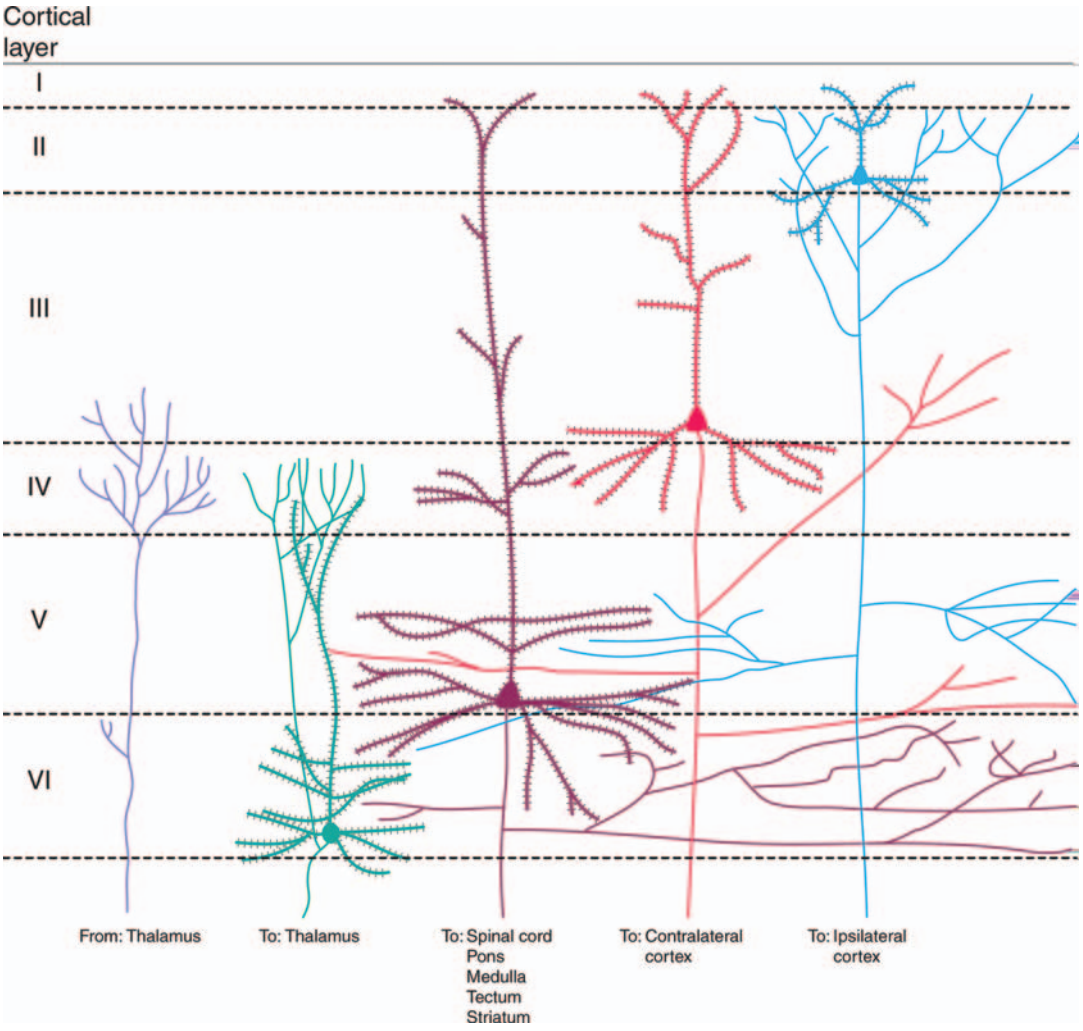


FIGURE 5.9 A schematic drawing of the six layers of cortex, the gray matter. Note that some cortical neurons send their axons to the thalamus, while others receive input from thalamic neurons. Ipsilateral = same side of the cortex; Contralateral = opposite side.

others receive input from thalamic neurons. Millions of cortical nerve cells go to the opposite hemisphere (the contralateral hemisphere), while many others project their axons to the same hemisphere (the ipsilateral side). However, the densest connections are to neighboring neurons. Cortical layer I consists largely of dendrites (input fibers) that are so densely packed and interconnected that this layer is sometimes called a 'feltwork', a woven sheet of dendrites. The neurons in this drawing (Figure 5.9) are called 'pyramidal' because their bodies look like microscopic pyramids. They are embedded in a matrix of glial cells, which are not shown here. These connection patterns in cortex undergo major change in human development and through-out the lifespan (see Chapter 15 for more discussion of this).

2.0 GROWING A BRAIN FROM THE BOTTOM UP

2.1 Evolution and personal history are expressed in the brain

We usually see the brain from the outside, so that the cortex is the most visible structure. But the brain grew and evolved from the inside out, very much like a tree, beginning from a single seed, then turning into a thin shoot, and then mushrooming in three directions: upward, forward, and outward from the axis of growth. That point applies both to phylogenesis – how species evolved – and ontogenesis – how the human brain grows from the fetus onward.

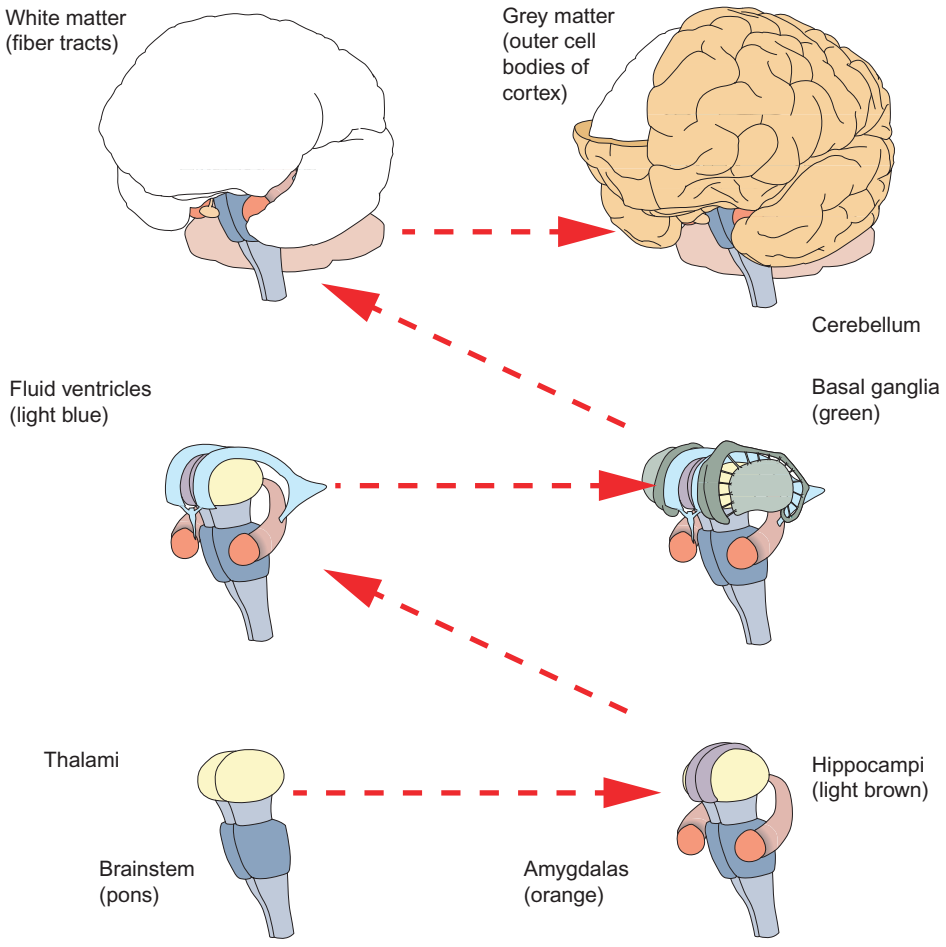


FIGURE 5.10 Growing the brain from the bottom up. If you can memorize these basic shapes, you will have a solid framework for understanding the brain. Notice how the brain builds on the brainstem, with the thalami on top as major input hub. The hippocampi and amygdalas are actually nestled inside each of the temporal lobes. The light blue fluid ventricles have no neurons, but provide the brain's own circulatory system. The basal ganglia can be thought of as the output hub of the system. A great deal of traffic flows back to the cortex as well. *Source*: Baars and Fu, with permission.

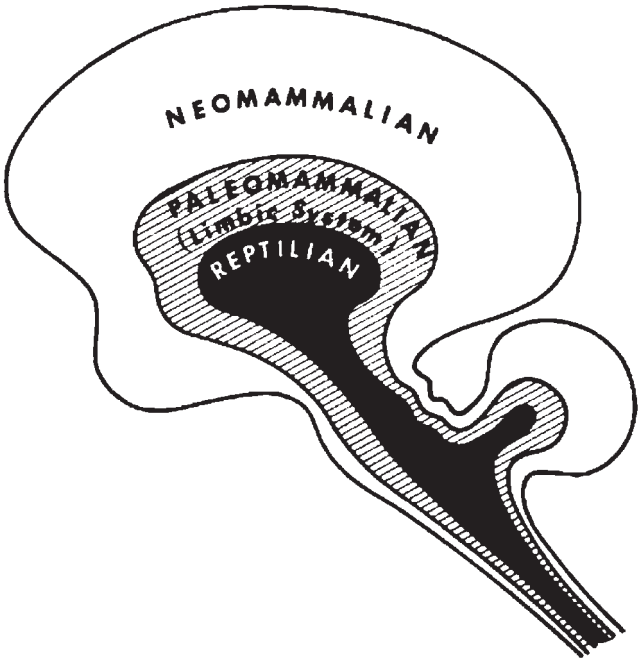


FIGURE 5.11 Diagram of the evolution of the mammalian brain. The forebrain evolves and expands along the lines of the three basic neural assemblies that anatomically and biochemically reflect ancestral commonalities with reptiles, early mammals, and late mammals. *Source*: Adapted from MacLean, 1967, with kind permission.

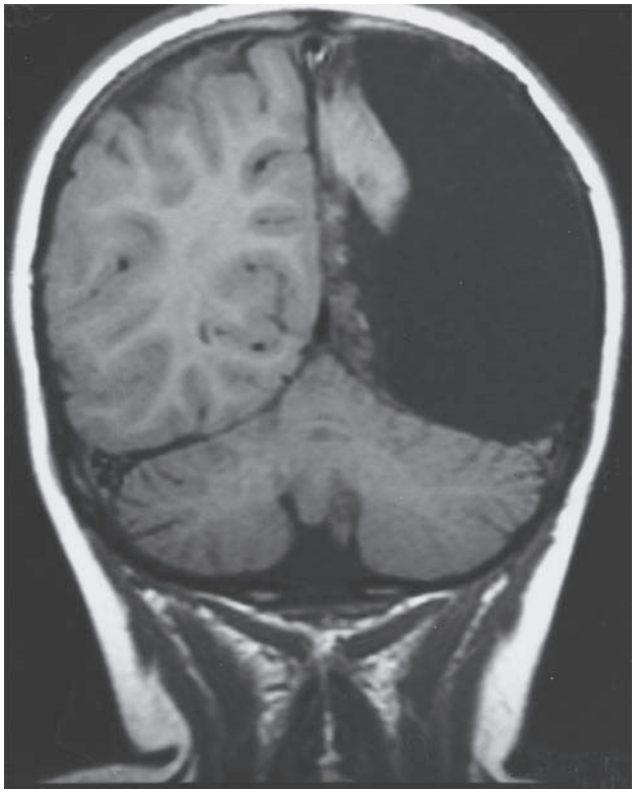


FIGURE 5.12 Do you really need a cortex? A structural brain scan (MRI) from a 7-year-old girl who had a surgical removal of her left hemisphere at age 3 for Rasmussen's encephalitis. Such surgeries can save children's lives if they are performed early enough. Because the brain is highly flexible at this age, the language capacity has shifted to the right hemisphere. Notice, however, that her brainstem and thalami are intact. The brainstem is crucial to life functions, and cannot be removed. She is able to play and talk, and has mild right side motor impairment. *Source*: Borgstein and Grotendorst, 2002.

The mature brain reveals that pattern of growth and evolution. It means, for example, that lower regions like the brainstem are generally more ancient than higher regions, such as the frontal cortex. Basic survival functions like breathing are controlled by neural centers in the lower brainstem, while the large prefrontal cortex in humans is a late addition to the basic mammalian brain plan. It is located the farthest upward and forward in the neural axis (Figure 5.11). Thus, local damage to prefrontal cortex has little impact on basic survival functions, but it can impair sophisticated abilities like decision-making, self-control, and even personality.

2.2 Building a brain from bottom to top

Because the brain involves hundreds of millions of years of evolutionary layering on top of older layers, the more recent levels hide the older ones. That is particularly true for the fast-ballooning neocortex in primates and humans, called the 'new cortex' because it is more recent, and has six layers rather than the four or five layers of the reptilian and early mammalian brain. The brain therefore grows a little bit like a mushroom over the course of evolutionary time. The neuraxis – the spinal cord and brain – grows from tiny cellular clumps, then forward into a slender cylindrical shoot, and then thickening centrifugally to form the spinal cord, covered by an approximate mushroom shape. In the womb, the embryonic brain develops into an S shape, and then the neocortex covers the older regions.

We can follow the brain from bottom to top to show structures that are normally hidden by the head of the mushroom. We encourage you to draw these successive levels of the great tower of the brain (Figure 5.10).

Unlike most other mammals, humans stand upright, and therefore bend their eyes and cortices at a right angle forward. That is why the upper direction of the human brain is both called 'dorsal', meaning 'toward the back' and also 'superior', meaning

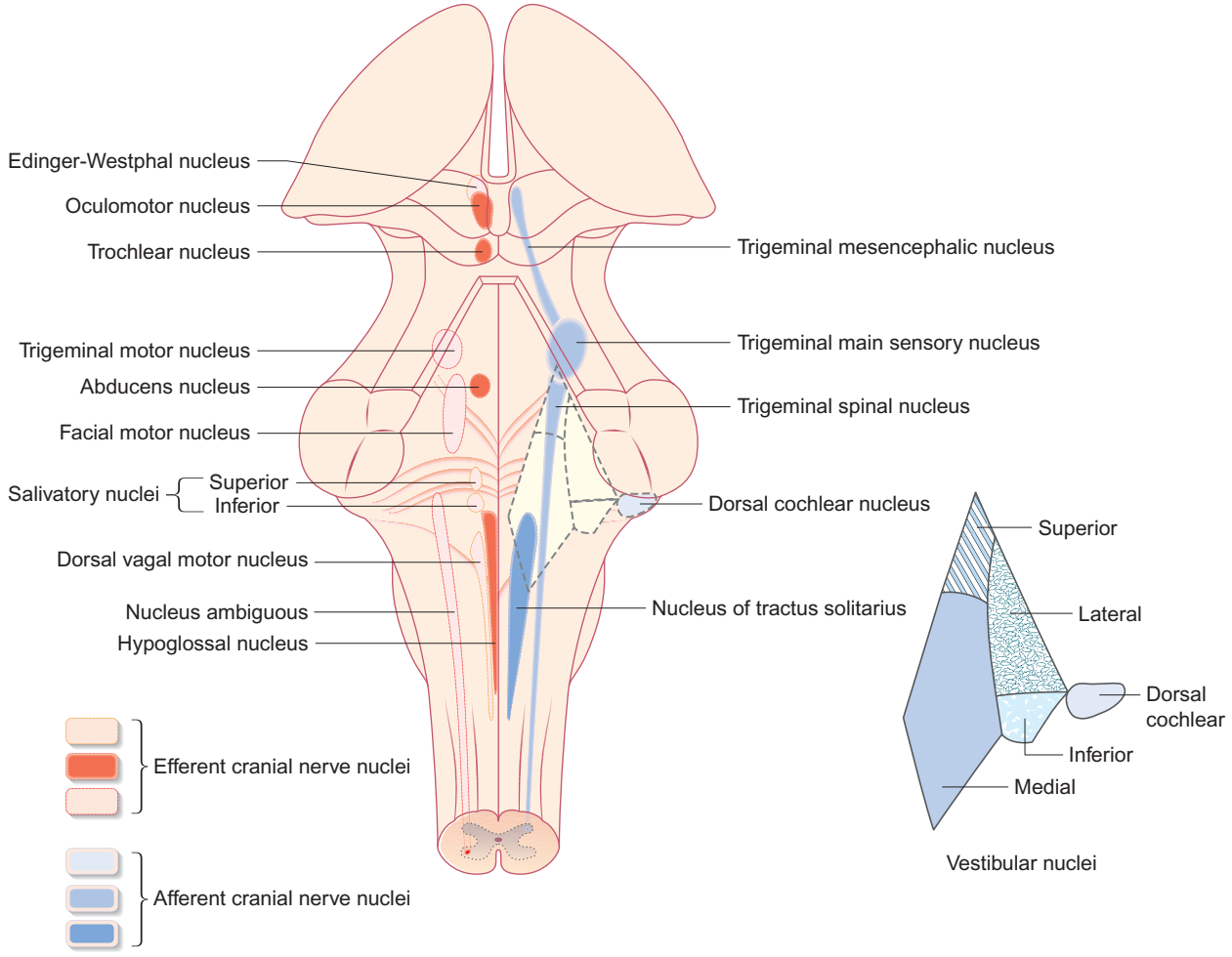


FIGURE 5.13 Detailed anatomy of the brainstem and pons. Notice that all the major input-output pathways of the brain emerge here, either flowing down the spinal cord, or out through narrow openings in the cranium. Vision, hearing, olfaction, and taste use cranial nerves as major pathways. Touch and pain perception in the head do the same. The brainstem also controls vital functions like breathing and heart rate. (Afferent = input to cortex; efferent = output from cortex). *Source*: Standring, 2005.

upward. The other directions are called 'ventral', 'toward the belly', and also 'inferior', meaning downward. We have a double vocabulary for the human brain, an important point to understand in order to avoid getting confused.

In this section, we will 'grow' a brain, beginning at the bottom with the older regions of the brain and layering on until we come to the newest part of the brain, the neocortex. We begin with the *brainstem* and *pons* which are at the bottom or 'oldest' section of the brain.

The brainstem (Figure 5.13) is continuous with the spinal cord. Its upper section, the pons, has nerve fibers that connect the two halves of the cerebellum. The brainstem and pons form a major route from the spinal cord to the brain. Some basic functions such as control of breathing and heart rate are controlled here.

Next, we have the *thalamus* – actually, they are the thalami, because there are two of them, one in each hemisphere (Figure 5.14). The two egg-shaped thalami form the upper end of the brainstem. The thalami are the great traffic hubs of the brain. They are also intimately connected with each great hemisphere.

Immediately below and in front of each thalamus is a cluster of nuclei called the *hypothalamus*. It is connected with the pituitary gland, often called the 'master gland' of the body (Figure 5.15). Together, the hypothalamus and pituitary are an extraordinarily important neurohormonal complex. Many types of physiological homeostasis are monitored by the hypothalamus. When hypothalamic neurons detect a deviation from the proper blood level of oxygen, they trigger increased breathing – such as the sigh you might make after reading intensively in a cramped

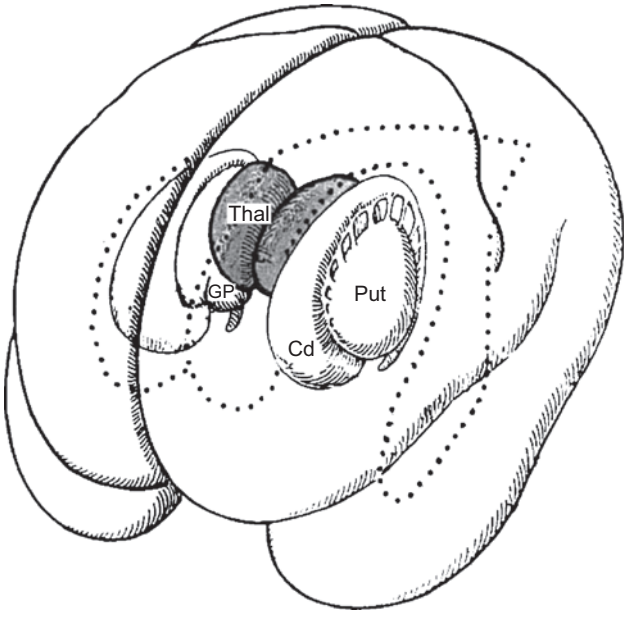


FIGURE 5.14 Transparent overview of the thalamus in the center of each hemisphere, and the basal ganglia looking like a 'shield and loop' on the outer side of each thalamus. *Source*: Ohye, 2002.

position. The hypothalamus also has crucial emotional functions.

Seated on top of the thalami like a rider on a horse are the two *hippocampi*, one on each side (Figures 5.10, 5.17). Each hippocampus is nestled inside of a temporal lobe on each side, as we will see later on. But it is important to see the doubled structure of two hippocampi. As we have seen, the hippocampus plays a major role in transferring experiential information to longer-term memory, and in retrieving episodic memories as well. It is also involved in spatial navigation.

Near the tip of each hippocampal loop is an almond-shaped structure called the *amygdala*, which plays a starring role in emotions and emotional association (Figure 5.18).

The next level up is deceiving. It looks like a neural structure but is not. It is the *four ventricles*, of which you can see the right and left one (Figure 5.10). The ventricles are small cavities containing a circulating fluid that is separate from the bloodstream. This brain-dedicated circulatory system descends into the spinal cord through a tiny tube called the aqueduct, and the fluid of the ventricular system is therefore called the cerebrospinal fluid. The ventricular walls have recently been found to be sites for neural stem cells, much to the surprise of many scientists. It was long believed that neurons could not be replaced during life, but certain regions like the hippocampus and olfactory surface replace their cells, just as the rest of the body does. The ventricular stem cells are believed to be a source of these new neurons.

Next up are the *basal ganglia*, literally, the clumps at the bottom of the brain (Figure 5.19). There is one outside of each thalamus. The elegant shield-like structure with outward radiating tubes is called the putamen. Looping over each is another artistic structure called the caudate nucleus. This 'shield and loop' structure is fundamentally important for control of movement and cognition. Notice that the basal ganglia are located outside of the thalami.

Finally, we can mount the two hemispheres on top of the lower levels of the brainstem, thalami, hippocampi and amygdala, ventricles and basal ganglia (Figure 5.20). So you should not be surprised when you carve away the cortex to see deeply buried, more ancient brain structures appear in the excavation.

One final note on 'growing' the brain: we present a bottom view of the brain in order to show you some brain regions that are difficult to see otherwise (Figure 5.21). You will notice the optic nerve linking the eyes, for example, to the cortex.

So there you have the brain, shown 'growing' from ancient areas to the neocortex in the two hemispheres. Now let's take a look at the functional significance of these brain areas in human cognition. In this discussion, we will proceed in a 'top down' fashion, beginning with the two hemispheres, moving through the major lobes, and then on to the subcortical 'satellites' of the brain.

3.0 FROM 'WHERE' TO 'WHAT': THE FUNCTIONAL ROLES OF BRAIN REGIONS

We have discussed the many levels of analysis with which to understand brain structure and shown where the major brain areas are located. Let's work through the brain now, beginning with the neocortex and ending with the brainstem, and discuss the functional roles they play in human cognition.

3.1 The cerebral hemispheres: the left-right division

The two mirror-image halves of the cortex have puzzled people for centuries. Why are there two hemispheres? If we have but one mind, why do we have

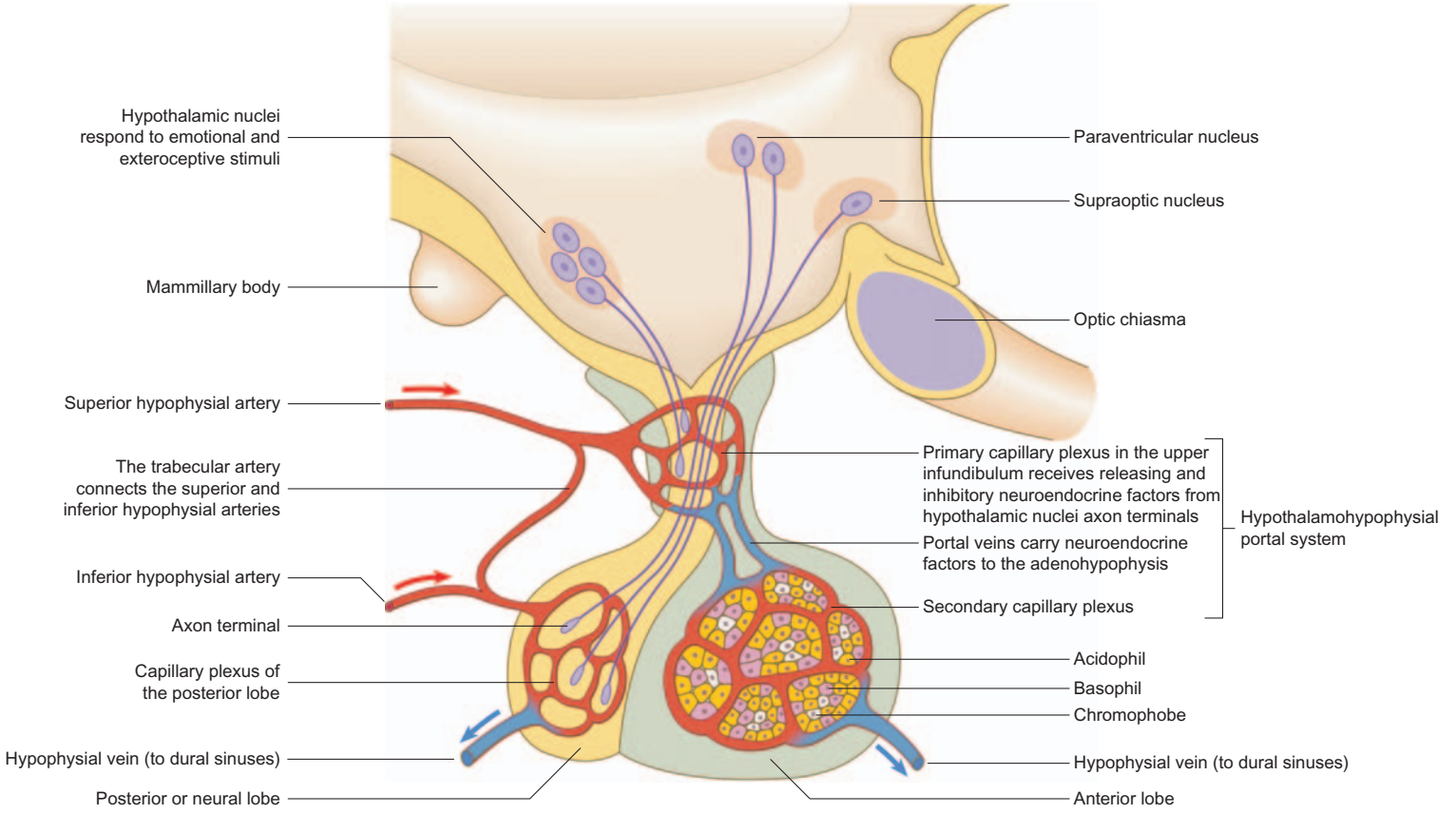


FIGURE 5.15 The hypothalamus (highlighted with dark blue circle) is a cluster of nuclei located immediately below and in front of each thalamus. The hypothalamus is important in regulating physiological and emotional processes and is closely connected with the pituitary gland. *Source*: Standring *et al.*, *Gray's Anatomy*, 2008, Chapter 21, Figure 21.11.

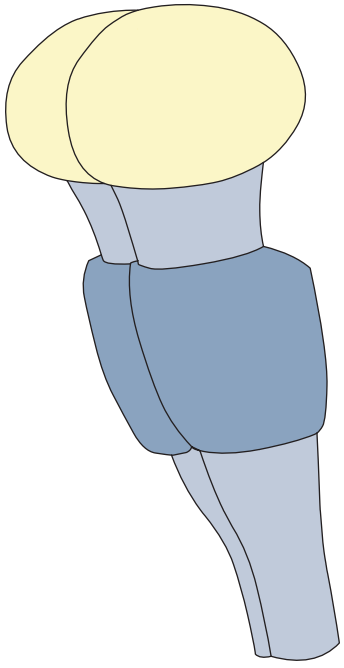


FIGURE 5.16 We begin 'growing' the brain with the brainstem and pons. *Source*: Baars and Fu.

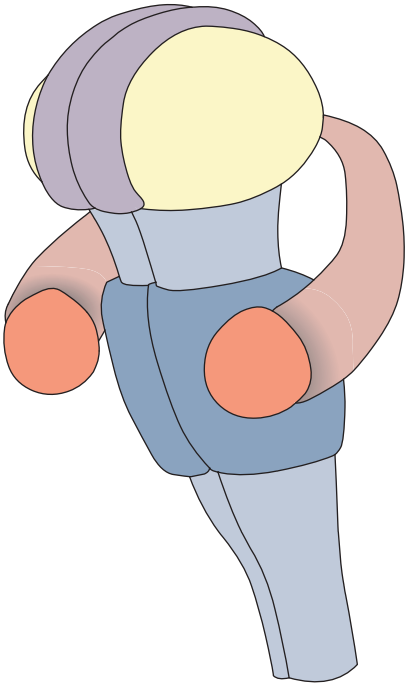


FIGURE 5.18 The amygdalas are situated just in front of the tip of each hippocampus. *Source*: Baars and Fu.

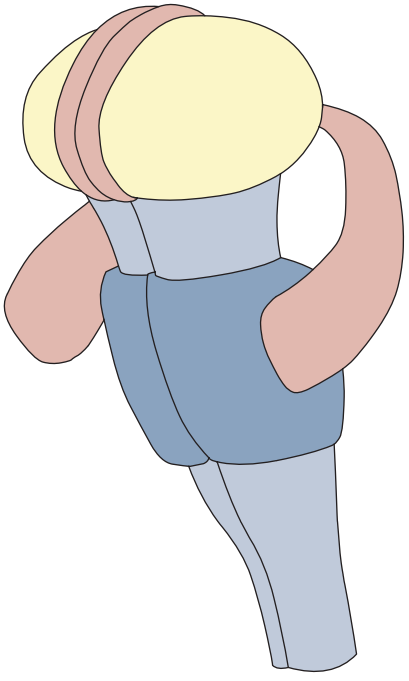


FIGURE 5.17 Schematic drawing of the hippocampi. *Source*: Baars and Fu.

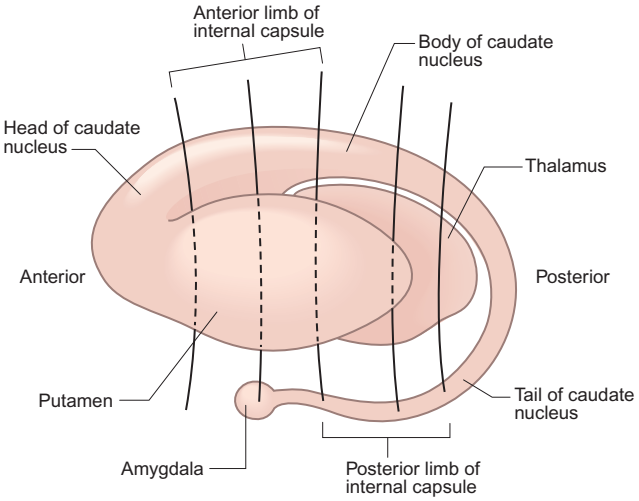


FIGURE 5.19 Side view of the basal ganglia, with the 'shield and loop' formed by the putamen and caudate nucleus, respectively. *Source*: Standring, 2005.

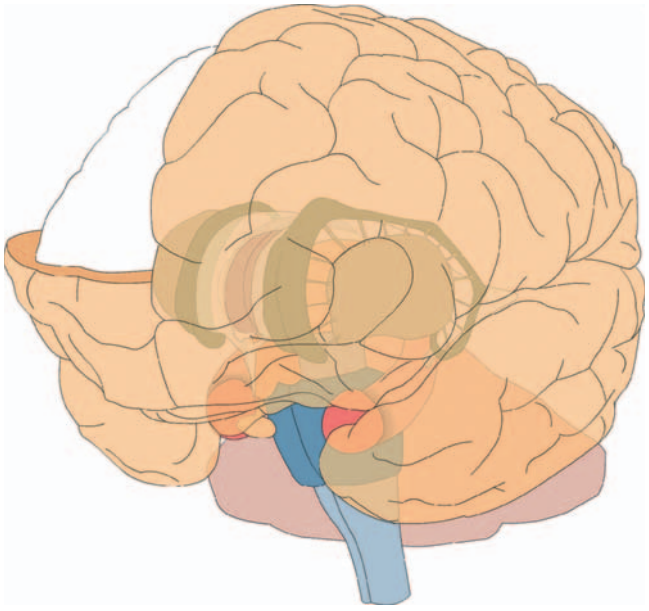


FIGURE 5.20 The cerebral hemispheres are shown mounted above the brainstem and other subcortical bodies. *Source*: Baars and Fu.

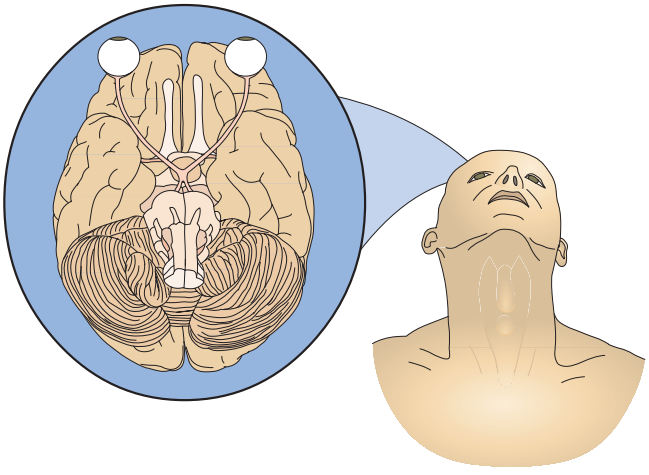


FIGURE 5.21 A view of the brain from below showing the medial temporal lobe and optic tracts. *Source*: Baars and Fu.

two hemispheres? Sir Charles Sherrington (1947) wrote:

> This self is a unity . . . it regards itself as one, others treat it as one. It is addressed as one, by a name to which it answers. The Law and the State schedule it as one. It and they identify it with a body which is considered by it and them to belong to it integrally. In short, unchallenged and unargued conviction assumes it to be one. The logic of grammar endorses this by a pronoun in the singular. All its diversity is merged in oneness.

The philosopher Rene Descartes, for example, was dumbfounded by the doubled nature of the brain.

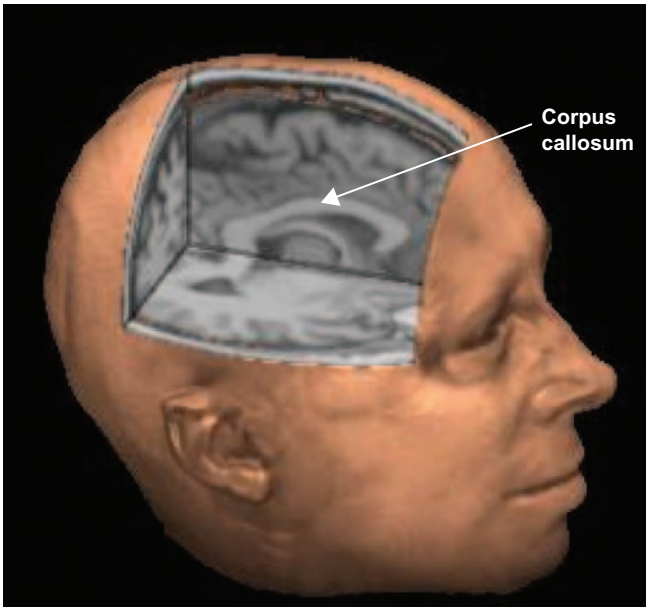


FIGURE 5.22 A cut-away of a three-dimensional magnetic resonance image showing the location of the corpus callosum – a white fiber arch extending horizontally from the anterior of the brain to the posterior, forming a fiber link between the two hemispheres. *Source*: Mark Dow, University of Oregon, with permission.

Because he believed that the soul must be a unitary whole, he looked for at least one brain structure that was not doubled, and finally decided on the small pineal gland at the back of the brainstem. There he believed the soul resided – roughly what we mean by subjective experience. Unfortunately for Descartes, when microscopes became powerful enough to examine the tiny pineal gland in detail, it also turned out to have two symmetrical halves, roughly mirror images of each other.

How do the two hemispheres 'talk' to each other? The answer lies in the fiber tract that runs from the front to the back of the brain, linking the two hemispheres.

3.1.1 The corpus callosum

The hemispheres are completely separate, divided by the longitudinal fissure that runs between the two hemispheres from the anterior (front) to the posterior (back) part of the brain. The link between the hemispheres is provided by the *corpus callosum*, a large arch of white matter (Figure 5.22). The number of axons traveling between the two hemispheres is estimated at more than 100 million. The corpus callosum has fibers that project between the hemispheres in an orderly way, with regions in the anterior portion connecting similar brain areas in the frontal lobes and regions in the posterior portion connecting similar brain areas in the occipital lobe.

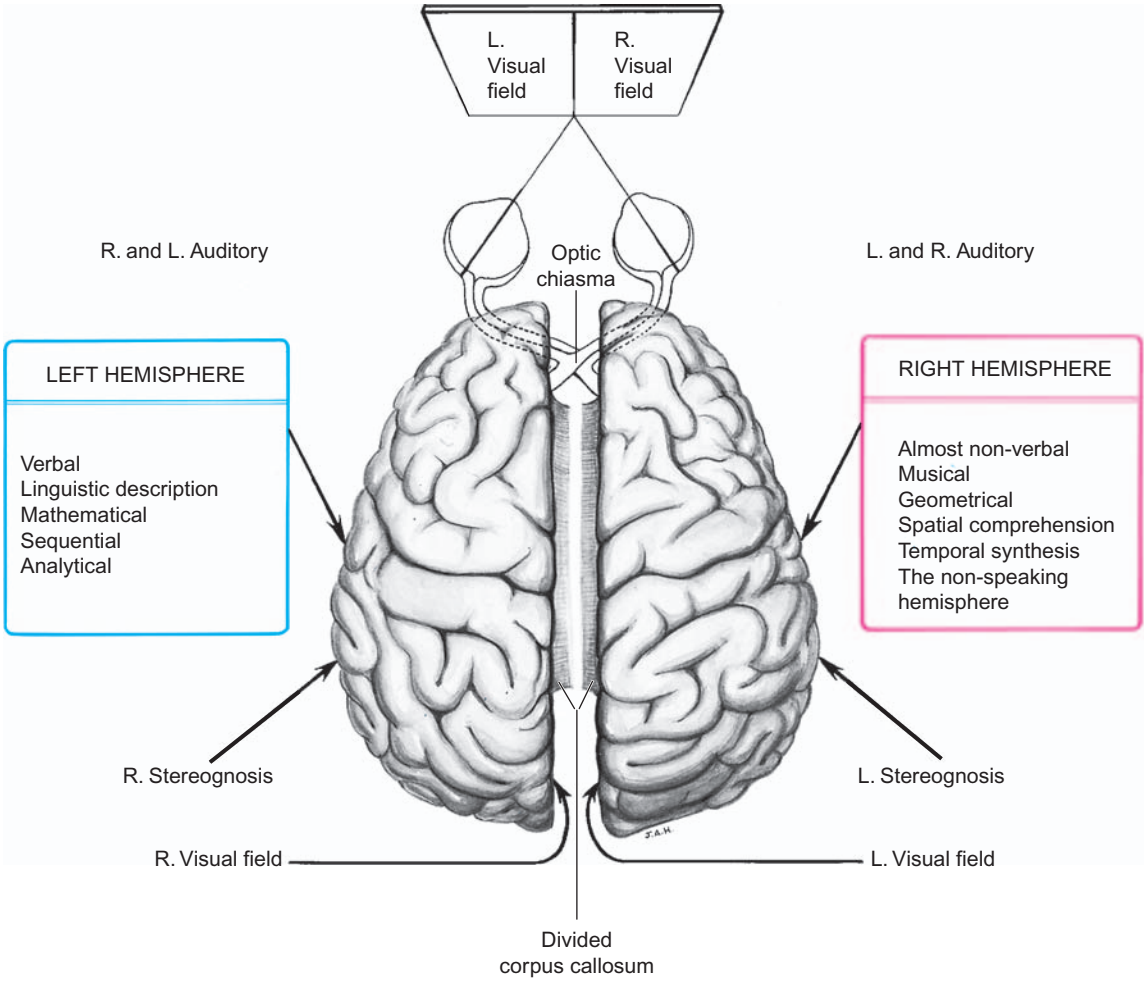


FIGURE 5.23 A top view of the two hemispheres. Schematic drawing of the two halves of the cerebral cortex, showing some major functions of the right and left hemispheres. Note the massive bridge of the corpus callosum connecting the two sides. The eyes on top focus on converging lines in order to enable stereoscopic depth perception. *Source:* Standring, 2005.

The role of the two hemispheres in human cognition and the mind-brain has been the subject of extensive study, and we are still unfolding the subtle and not-so-subtle differences in the roles that the mirror-image hemispheres play in perception, language, thought, and consciousness. There are some hemispheric differences that are fairly well understood, such as crossover wiring. Many aspects of sensory and motor processing entail the crossing over of input (sensory) or output (motor) information from the left side to the right, and vice versa (Figure 5.23).

For example, each optic nerve coming from the retina is split into a nasal half (on each side of the nose), which crosses over to the opposite side of the brain, and a lateral half, which proceeds to the same side (ipsilaterally). Only the olfactory nerve, which is a very ancient sensory system, stays on the same side of the brain on its way to cortex. The cortical output control of the hands is also crossed over, with the left hemisphere controlling the right hand, and the right controlling the left hand (Figure 5.24). While the left and right hemispheres have some different functions, the corpus callosum has some 100 million fibers, constantly trafficking back and forth, which serves to integrate information from both sides. The time lag between the two hemispheres working on the same task may be as short as 10 ms, or one-hundredth of a second (Handy *et al.*, 2003). Therefore, when the great information highway of the corpus callosum is intact, the differences between the hemispheres are not very obvious. But when it is cut, and the proper experimental controls are used to separate the input of the right and left half of each eye's visual field, suddenly major hemispheric differences become observable.

The question of the perceived unity of the world continues to interest scientists. The most spectacular finding in that respect has been the discovery that the

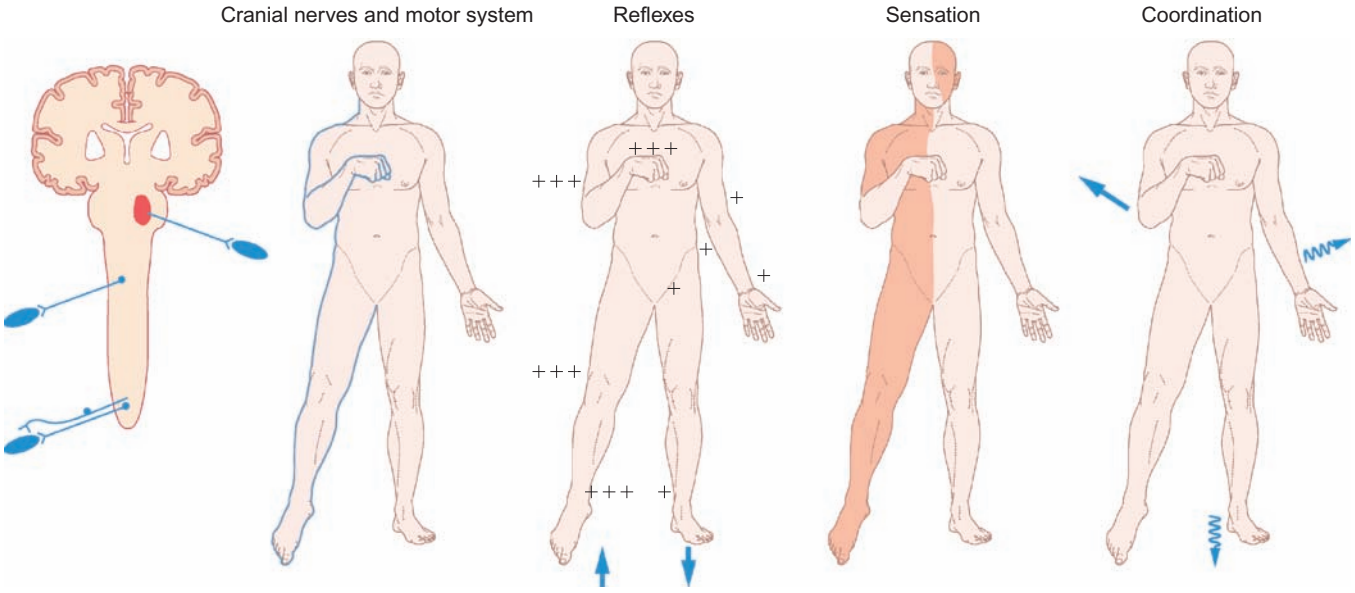


FIGURE 5.24 The pattern of cortical control over regions of the body. Notice that sensation and cortical motor control pathways cross over in the brain. Simple reflexes do not cross over, and coordination involves interaction between both sides. *Source:* Standring, 2005.

corpus callosum can be cut in humans, without changing the perceived unity of the world and of the self. Indeed, for many years such callosectomies (separation or cutting the corpus callosum) were performed to improve uncontrollable epilepsy. A complete slicing of the corpus callosum is called a callosotomy; more common, today, is a partial cut of only the regions of the two hemispheres that spread epileptic seizure activity. This partial cut is called a callosectomy. Doctors and their patients believed that cutting some 100 million fibers in the corpus callosum had no noticeable effect at all! It is a dramatic illustration of the capacity of the brain to adapt to quite severe damage – to fill in the missing details of the experienced world by means of eye movements, for example. More careful study, however, has provided evidence that a complete slicing, a callosotomy does have subtle but long-lasting effects and so a partial resection, or callosectomy, is preferred.

FRONTIERS OF COGNITIVE NEUROSCIENCE

Synesthesia

FIGURE 5.25 David Eagleman, PhD, Department of Neuroscience, Baylor College of Medicine, Houston, Texas, USA

Imagine a world of magenta Tuesdays, tastes that have shapes, and wavy green symphonies. One in a hundred otherwise ordinary people experience the world this way, in a condition called *synesthesia* – the fusion of different sense experiences. In synesthesia, stimulation of one sense triggers an experience in a different sense. For example, a voice or the sound of music are not just heard but also seen, tasted, or felt as a touch. Synesthesia is a fusion of different sensory perceptions: the feel of sandpaper might evoke the musical sound of F-sharp, a symphony might be experienced in blue and gold colors, or the concept of February might be experienced as being located above one's right shoulder. Most *synesthetes* (people with synesthesia) are unaware that their experiences are in any way unusual.

Synesthesia comes in many varieties, and having one type gives you a high chance of having a second or third type. Experiencing the days of the week in color is the most common kind of synesthesia, followed by colored letters and numbers. Other common varieties include tasted words, colored hearing, number-lines perceived in three dimensions, and the personification of letters and numerals.

Synesthetic perceptions are involuntary, automatic, and generally consistent over time. Moreover, synesthetic perceptions are typically intrinsic, meaning that what is sensed is something like a simple color, shape, or texture, rather than something that is a thought association. Synesthetes don't say, "This music makes me experience a vase of flowers on a restaurant table." It just happens to them.

Synesthesia seems to be the result of increased cross-talk among sensory areas in the brain – like neighboring countries with porous borders on the brain's map. Synesthesia has fascinated laypersons and scientists alike with its wealth of sensory amalgamations, but only recently has it been appreciated how the brains of such individuals yield surprising insights into normal brain function.

Although synesthesia has been explored in behavioral and neuroimaging experiments, its genetic basis remains unknown. My laboratory group realized that synesthesia is an ideal condition for genetic analysis, for three reasons: (1) synesthesia clusters in families and appears to be inherited; (2) synesthetic perception results from increased cross-talk between neural areas, which suggests a set of candidate genes; and (3) a battery of tests developed in our lab allows for confident identification of real synesthetes, not just people who have free associations to their experiences.

We therefore are performing a large-scale genetic study, called a family linkage analysis, to map the gene(s) that correlate with color synesthesias. To this end, we have developed a battery of tests to clearly identify synesthetes; that is, to distinguish them from control subjects. These tests are offered free to the research community at www.synesthete.org. Several families with multiple synesthetes have provided pedigrees, and we have harvested DNA samples from over 100 people in these families. A genomewide scan is identifying the most probable genetic region responsible for synesthesia in these families. Understanding the genetic basis of synesthesia yields insight into the way normal brains are wired. And it demonstrates that more than one kind of brain – and one kind of mind – is possible.

Synesthesia affects the brain wiring of one in several hundred people, making it far more common than originally thought, and far more important scientifically than a mere curiosity. Other evidence suggests that we may all be synesthetic to some extent – but the majority of us remains unconscious of the sensory fusions going on in our brains.

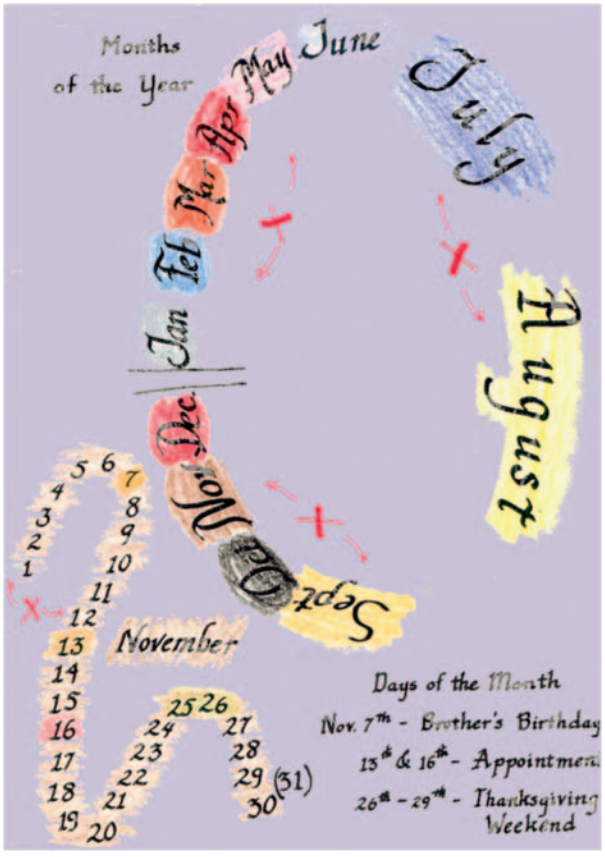


FIGURE 5.26 In a common form of synesthesia, months and days of the month can have both colors and specific spatial configurations. *Source*: Cytowic and Eagleman, 2009 in *Wednesday is Indigo Blue: Discovering the Brain of Synesthesia*. Cambridge: MIT Press.

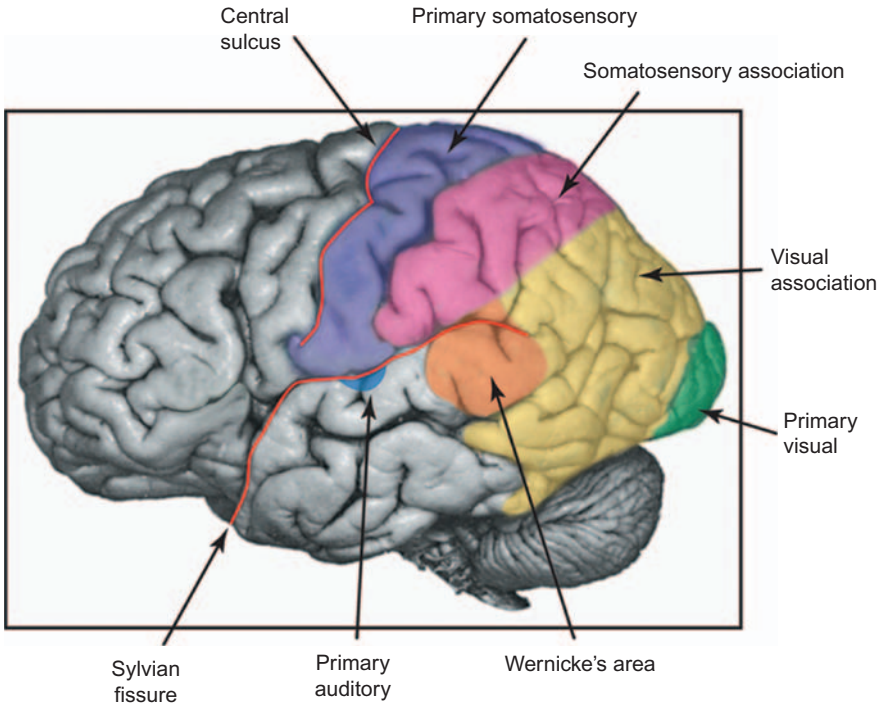


FIGURE 5.27 A view of functional areas in some of the sensory regions of the cortex. The central sulcus is seen separating the frontal lobe from the parietal lobe. Immediately posterior to the central sulcus is the primary somatosensory area. The Sylvian fissure is also called the *lateral fissure*. *Source*: Squire *et al.*, 2008.

3.2 Output and input: the front-back division

The cortex is a folded sheet of gray matter that would measure roughly 2 feet by 2 feet (60 cm by 60 cm) if it were unfolded. To fit within the skull, the cortex is folded into hills (gyri) and valleys (sulci). The cortex contains four lobes that are visible from the outside and two large regions that are not visible. Before we discuss the functions of these regions, let's take a look at another major division of the brain: the front-back division of the cerebral cortex. In order to understand this division, you will need to be able to locate some landmarks in the brain. In Figure 5.27, see if you can locate the *central sulcus* that runs vertically between the frontal lobe and the parietal lobe. To locate it, look for the region labeled 'primary somatosensory'. The central sulcus is just in front of, or anterior to, this region. The second landmark to look for is the *Sylvian fissure*. It runs more or less horizontally from the frontal lobe posterior, separating the temporal lobe from the parietal and frontal lobes.

The sensory – or input – regions of the cortex are located posterior to the central sulcus and the Sylvian fissure, in the parietal, temporal, and occipital lobes. These lobes contain the visual cortex, auditory cortex, and somatosensory cortex, where information coming from the eyes, ears, and body is processed. The visual cortex, for example, begins in the occipital lobe but extends to the parietal and temporal lobes. The auditory cortex is located in the temporal lobe but also extends to the parietal lobe. Somatosensory areas are located in the parietal lobe. Taste and smell regions are located at the bottom of the temporal lobes. This 'back of the brain' large region, encompassing three cortical lobes, is not simply a site for processing sensory information. It is also the region of cortex for associative processes, where information from the various senses is 'bound together' for higher order processing. Think about watching a movie – these association areas will help you understand how to relate what you are hearing to what you are seeing on the screen. Much of this type of processing occurs in the parietal lobe, and we will discuss this important lobe in more detail in the next section. These association regions are largest in primates and largest of all in humans.

The motor – or output – regions of the cortex are located in the frontal lobe, anterior to the central sulcus and the Sylvian fissure. Look again at Figure 5.27 and locate the region labeled 'primary somatosensory', just posterior to the central sulcus. Although it is not labeled on this figure, the primary motor region is in the frontal lobe, just across the central sulcus and anterior to the somatosensory regions in the parietal lobe. The close physical connection between the somatosensory cortex and the motor cortex allows for a tight coupling between the senses of touch, pressure,

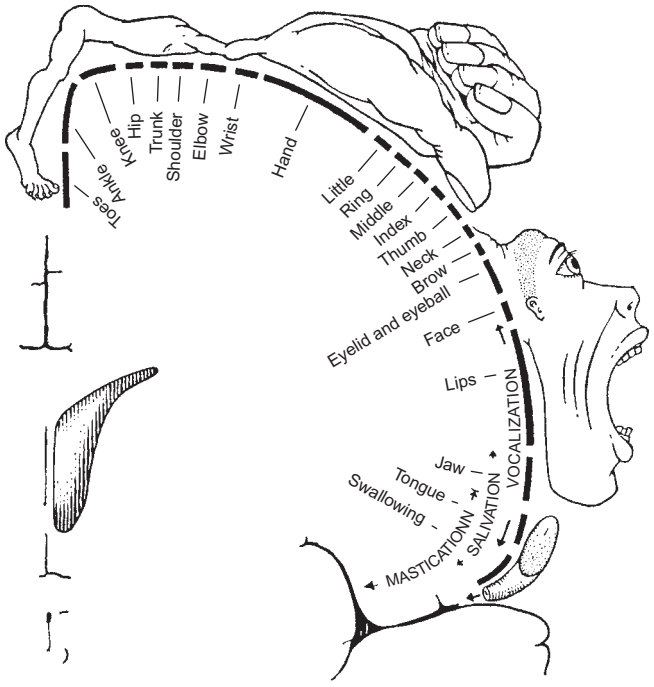


FIGURE 5.28 Drawing of the somatosensory homunculus, showing the representation of body areas in the cortex. Note that some body areas, such as the face, have a disproportionately larger representation than other areas, such as the trunk. *Source*: Standring, 2005.

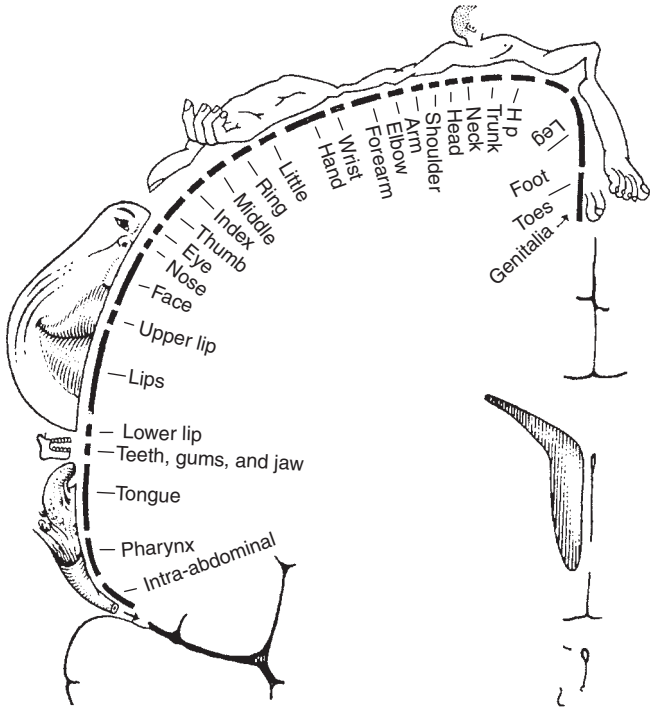


FIGURE 5.29 Drawing of the motor homunculus, showing the representation of body areas in motor cortex. Note that some body areas, such as the face, have a disproportionately larger representation than other areas, such as the trunk. *Source*: Standring, 2005.

and pain and the action or motor system. In fact, there is an intricate mapping of the body that is reflected in similar ways in the somatosensory region located just posterior to the central sulcus and its corresponding motor region located just anterior. This intricate mapping is a representation of areas of the body: the different regions of the body are not equally represented in these cortical regions; some areas, such as the face and hands, have quite a disproportionately large representation and other regions, such as the center of the back, have a disproportionately small representation. Consider how much more sensitive your fingertips are to touch, pressure, and pain than, say, the small of your back. The representational map in cortex reflects this differing sensitivity. There are two maps of the body: one is in somatosensory cortex and a very similar one is in motor cortex (Figures 5.28 and 5.29).

These two body maps or homunculi ('little men') were first discovered by the pioneer neurosurgeon Wilder Penfield at the University of Montreal in the 1950s and 1960s. Penfield's team was the first to stimulate the cortex of awake patients, which is possible because the cortical surface contains no pain receptors. Therefore, local anesthetic applied to the incision was enough to dull the pain of the removal of the scalp, and surgeons could electrically stimulate the exposed cortical surface and ask their awake patients about their experiences as a result. Their discoveries have largely stood the test of time. Exploration by electrical stimulation was medically necessary in order to know where to operate in the brain while minimizing damage to functional regions in patients. In the case of the sensory homunculus (somatosensory), local stimulation would evoke feelings of touch in the corresponding part of the body. Stimulation of the motor homunculus would evoke specific body movements, but interestingly, patients would deny a sense of ownership of those movements. When Penfield would ask, 'Are you moving your hand?' when stimulating the hand region, a patient might say, 'No, doctor, you're moving my hand'. If, however, the surgeon moved perhaps a centimeter forward to the pre-motor strip, stimulation would evoke a reported intention to move one's body, without a sense of being externally controlled. It is a fundamental distinction, which we will return to later.

The essential point here is that the central sulcus is an important landmark to know. Not only does it separate the sensory and motor homunculi but, more broadly, the central sulcus separates the more sensory

half of cortex (posterior), from the frontal half (anterior). Posterior cortex contains the projection regions of the major sense organs – vision, hearing, touch, smell, taste. In contrast, frontal cortex is involved in action control, planning, some working memory functions, language production, and the like. In a sense, the posterior half deals with the perceptual present, while the anterior half tries to predict and control the future.

3.3 The major lobes: visible and hidden

We have used the analogy of the geography of the brain. In this setting, the major lobes can be viewed as large continents in brain geography. While each is separate from the other and has its own local functions and anatomical features, each is part of the whole, the brain, and thus is united and intimately linked to total brain function. The four 'continents' of the brain are shown in Figure 5.30 and include the frontal, parietal, temporal, and occipital lobes. In this section, we will discuss their functional roles in cognition. Two other major regions, not visible from the exterior view of the brain, play important roles in cognition and we will describe those as well.

3.3.1 Frontal lobe

The massive frontal lobe is the site for motor planning and motor output. As we mentioned, the motor areas are tightly connected to the somatosensory regions with similar homunculus maps representing body areas. These motor functions that are present in the human brain are present in most mammalian brains in a similar way. But the frontal lobe in humans is far larger than in non-human primates or any other creature. What other functions does the frontal lobe perform and how is its role unique in humans?

The frontal lobe has been termed the 'organ of civilization' (Luria, 1966). The regions of the frontal lobe that have earned this term are primarily in the prefrontal cortex. The prefrontal cortex is located on the medial, lateral, and orbital surfaces of the most anterior portion of the frontal lobe (Figure 5.31).

Prefrontal cortex is the non-motor part of frontal cortex. Notice that prefrontal cortex is the most forward part of the frontal cortex. The term 'prefrontal' is somewhat confusing, but it means 'at the front of the frontal cortex'. There are no obvious boundary markers for prefrontal cortex, which is defined instead by a set of projections from the thalamus. Nevertheless, prefrontal cortex is perhaps the most distinctively 'cognitive'

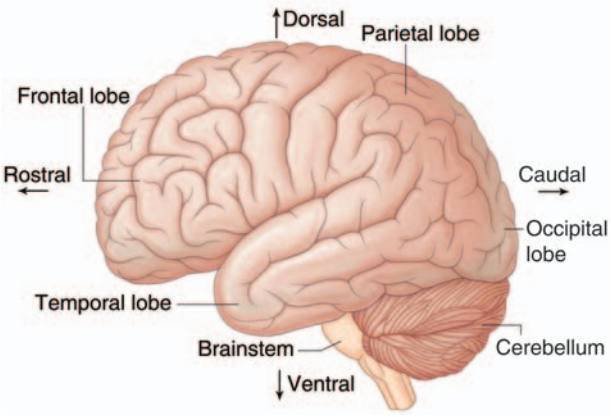


FIGURE 5.30 Basic brain directions. Because the human brain is rotated 90 degrees forward from the spinal cord (unlike most mammals and reptiles), it has two sets of labels. The dorsal direction is also called superior, the ventral is also called inferior, and rostral, roughly the same as frontal and caudal, is sometimes called posterior. To simplify, just use plain language, like front, back, upper, and lower. *Source*: Standring, 2005.

part of the brain. The prefrontal cortex is a large cortical region, taking up an estimated one-third of the entire area of cortex. What is the prefrontal cortex specialized for and why is it so uniquely a human region?

The prefrontal cortex is specifically needed for:

- initiating activities
- planning
- holding critical information ready to use (an aspect of working memory)
- changing mental set from one line of thinking to another
- monitoring the effectiveness of one's actions
- detecting and resolving conflicting plans for action
- inhibiting plans and actions that are ineffective or self-defeating.

This list shows how important the prefrontal cortex is to human cognition. Many anatomists believe that prefrontal cortex is largest in humans, and distinguishes our species from other primates. In addition, the prefrontal cortex has regions for emotional and personality processes as well as social cognition – knowing 'how to behave' for example. On the lateral convexity, interposed between the dorsolateral prefrontal and the ventral portion of premotor cortex, is Broca's area. This area is involved in the abstract mediation of the verbal expression of language, a uniquely human function.

The frontal lobe, then, is far larger in humans than other primates and has developed many new functions and processes for dealing with human activities such as language, thought, and executive control of higher

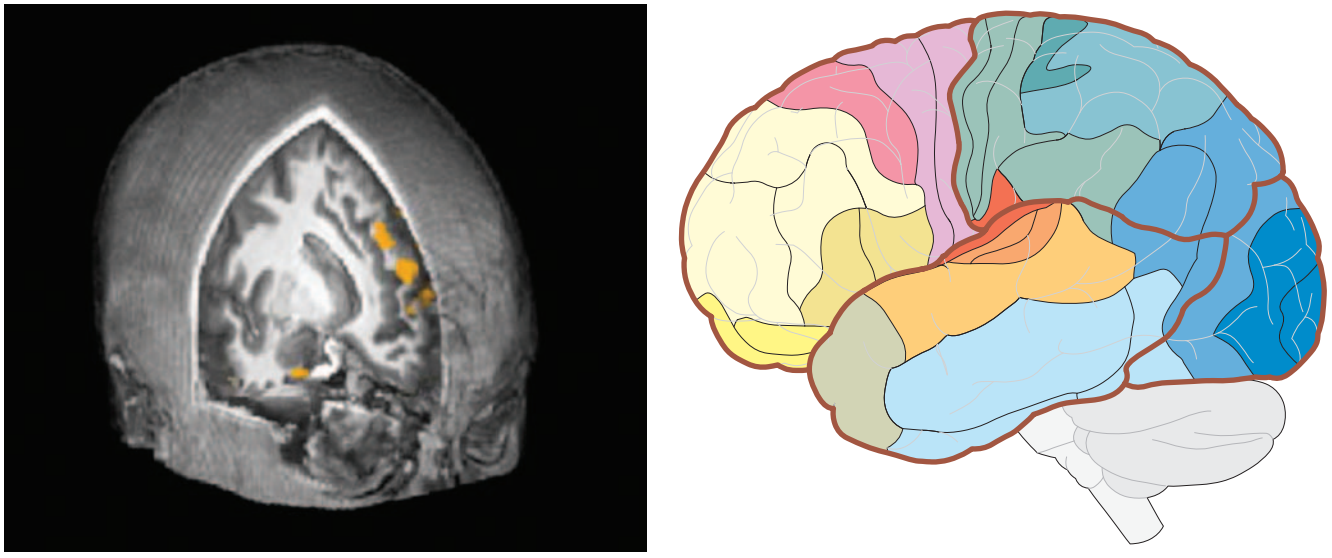


FIGURE 5.31 *Left:* An activation map rendered on a three-dimensional magnetic resonance image showing regions in the medial prefrontal cortex. *Right:* How to find the prefrontal cortex. The entire frontal cortex is in front of the central sulcus, the vertical fold that runs from the top of the cortex down to the temporal lobe. Locate the central sulcus in this figure. The two purple gyri (hills) immediately in front of the central sulcus are called the motor and premotor cortex. The reddish-purple patch in front of that is called the supplementary motor cortex. However, the three shades of yellow in the frontal third of the whole cortex is prefrontal cortex, often considered the most 'cognitive' part of the brain. *Source*: Harenski and Hamann, 2006.

order processes. A second lobe that has also evolved to be much larger in humans is the parietal lobe and we will see what functions it performs in the next section.

3.3.2 Parietal lobe

As we noted earlier, the anterior region of the parietal lobe holds the somatosensory cortex. However, the parietal lobe is not just a somatosensory region in humans, much as the frontal lobe is not just a motor region. One important function of the parietal lobe is multiple maps of body space. What does 'body space' mean exactly? Think about sitting in a chair at a table and looking down at your hands. Your eyes bring sensory input to your brain about where your hands are in respect to your body, but there are other inputs telling you where you hands are as well (which is why you know where your hands are even if your eyes are closed). Your imagined hand position will be from your own perspective, or the *egocentric* perspective. Now imagine a friend sitting across the table from you and conjure up where your hands are from his or her perspective. How do you do this? It is easy to accomplish and regions in the parietal lobe are where this type of processing take place (Figure 5.32).

Posterior and inferior to the somatosensory region is an area termed the inferior parietal lobe or IPL. The functional significance of this region is still being elucidated. However, it is thought to be the site for multisensory integration.

3.3.3 Temporal lobe

The temporal lobe is the region where sound is processed and, not surprisingly, it is also a region where auditory language and speech comprehension systems are located. The auditory cortex is located on the upper banks of the temporal lobe and within the Sylvian fissure. Just posterior to the auditory cortex is Wernicke's area for speech comprehension. But the temporal lobe is not only a sound and language processing region. The middle sections of the temporal lobe are thought to contain conceptual representations for semantic knowledge. More inferior and posterior temporal lobe areas are more finely tuned for representing visual objects and include the fusiform face area.

3.3.4 Occipital lobe

The occipital lobe, at the very posterior region of cortex, is home to visual cortex. Most of visual cortex is hidden within the calcarine fissure. The visual system occupies a large area within the occipital lobe that extends anterior to the parietal and temporal lobes. New techniques provide the ability to 'inflate' these cortical regions to remove the folds and allow us to see the functional

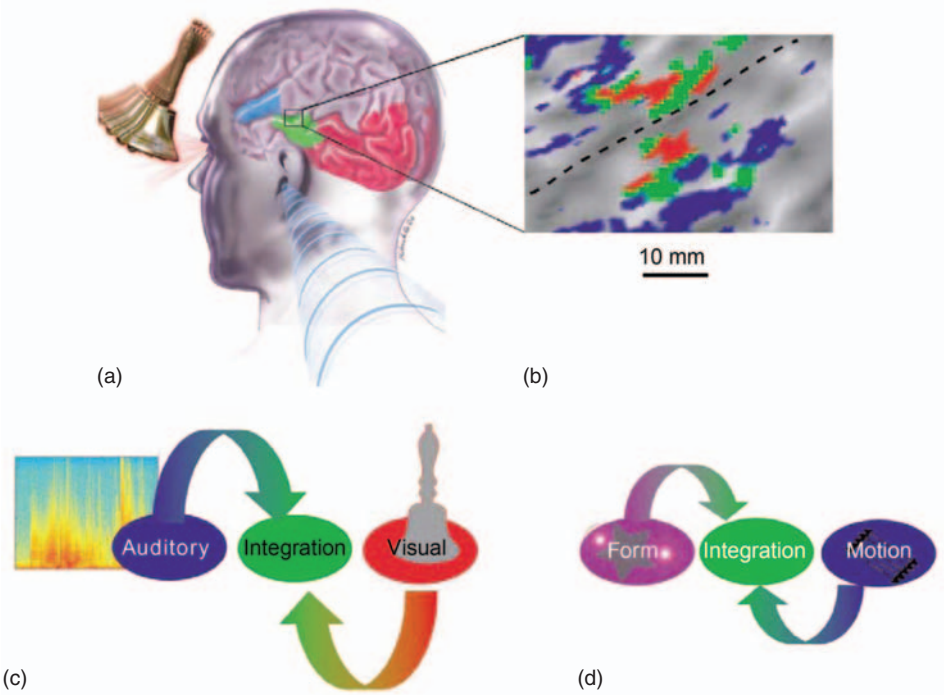


FIGURE 5.32 Schematic of some of the multisensory functions of the parietal lobe. The sight and sound of the bell are combined by neurons in the parietal cortex, using a 'map' of the space surrounding the body (egocentric space). *Source*: Beauchamp, 2005.

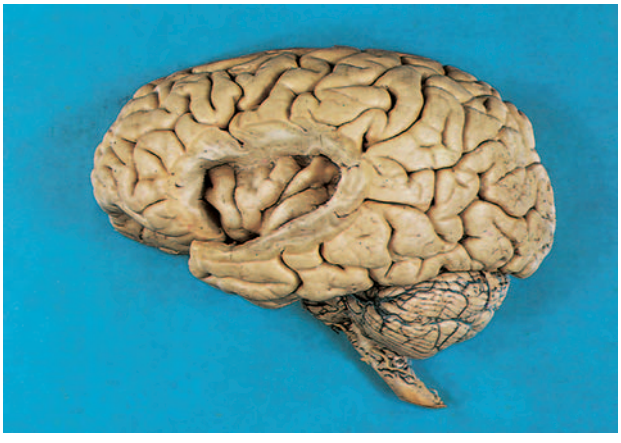


FIGURE 5.33 An actual human brain, showing the insula just above and hidden behind the temporal lobe. *Source*: Standring, 2005.

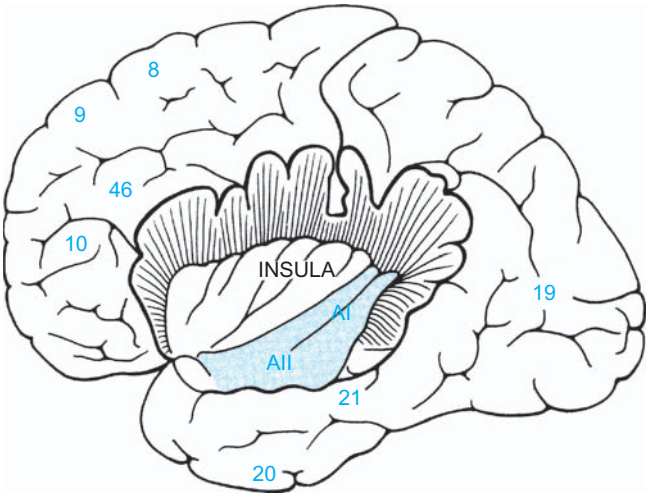


FIGURE 5.34 A cut-away view of the left hemisphere revealing the insula, which is not visible from a lateral view. 'Insula' means 'island' because of this appearance when the brain is dissected. *Source*: Standring, 2005.

visual regions that are normally tucked into the calcarine fissure and difficult to see on a brain scan.

3.3.5 The insula and Sylvian fissure

Like a large tree, the cortex has grown to cover up large parts of itself, as we can see by inflating the cortex mathematically and spreading it into a flat sheet. Two of the areas that are hidden by the expanding cortex are especially important: the *insula* and the Sylvian fissure. When the temporal lobe is gently pulled away from the rest of cortex, a new hidden world appears. This region is called the 'insula', or 'island', because it appears like a separate island of cortex (Figures 5.33 and 5.34). The

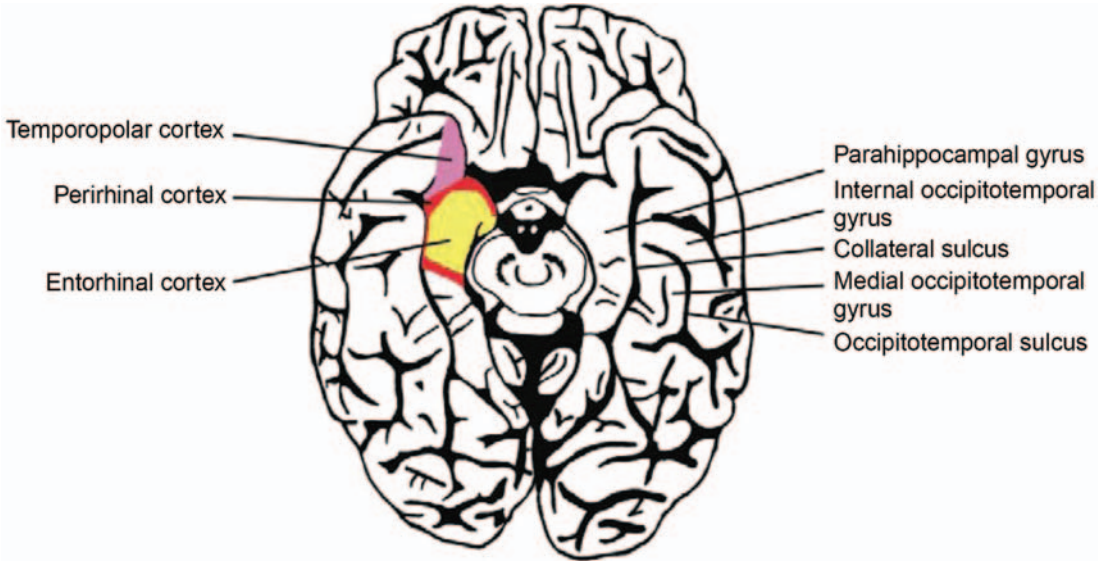


FIGURE 5.35 The medial temporal lobe (MTL) – the midline regions seen from the bottom. This is the ancient 'smell brain' which is now surmounted by a massive 'new' cortex in higher mammals. It is therefore difficult to see from the outside, but it still retains many essential functions, including encoding conscious events into memories (episodic memories). *Source*: Buckley and Gaffen, 2006.

insula is not often seen in popular accounts of the brain, but it involves hundreds of millions of neurons and quite a wide expanse of cortical surface. Neurological evidence suggests that it may be involved in 'gut feelings' like the conscious sense of nausea and disgust. But the insula is so large that it probably has multiple functions. There does seem to be good convergent evidence that interoception – feelings of one's inner organs – may be one of the major roles of the secret island of cortex.

One researcher suggests that: 'In humans, . . . the right anterior insula, . . . seems to provide the basis for the subjective image of the material self as a feeling (sentient) entity, that is, emotional awareness' (Craig, 2005).

The Sylvian fissure is a very large sulcus that runs in a roughly horizontal direction from the frontal lobe, between the parietal and temporal lobes, ending near the junction of the parietal, temporal, and occipital lobes. The anatomy of the fissure differs widely across individuals and also between hemispheres. Tucked inside the Sylvian fissure, on the upper banks of the superior temporal gyrus, is the *supratemporal plane*. This region is called a plane because is it a somewhat flat bank of cortex extending from the lateral surface into the medial regions. The supratemporal plane is home to primary and secondary auditory cortex as well as parts of Wernicke's area for speech comprehension. The upper bank of the Sylvian fissure, adjacent to the parietal lobe and opposite the supratemporal plane, is home to somatosensory cortex that wraps around and under the top section of the fissure.

3.3.6 The medial temporal lobe

The *medial temporal lobe* (MTL) is actually part of the temporal lobe, but its function and anatomy differ strikingly and it is typically referred to as a separate structure. The MTL is home to the hippocampi and related regions that are associated with memory functions (Figure 5.35). There are many regions in the MTL, including a region called the *limbic* area. The word 'limbus' means 'boundary', and true to its name, there is a great deal of debate about the proper boundaries of this region. You will occasionally see the entire complex of hippocampus, amygdala, and limbic cortex being called the 'limbic system'. All these terms have their uses, and it is just important to be aware of what is intended.

The upper arc is called the cingulate gyrus ('cingulum' means belt or sash as in 'cinch'), which is nestled between the corpus callosum and the cingulate sulcus (Figure 5.36). The front half of this region generally lights up in brain scans during tasks that involve conflicting stimuli or responses, a very important aspect of executive function. In the classical Stroop effect, for example, there is a conflict between the color of words and the meaning of the same words. The front half of

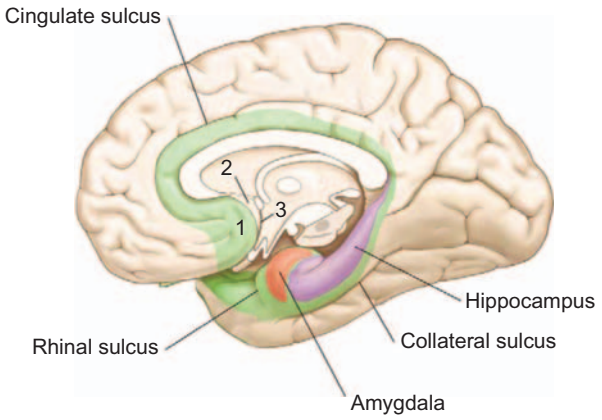


FIGURE 5.36 The medial temporal lobe and cingulate gyrus (green upper loop), seen from the midline section of the brain. The hippocampus is colored purple and amygdala orange. They are actually embedded inside of the temporal lobe. *Source*: Heimer and Van Hoesen, 2006.

the cingulate is somehow involved in detecting or resolving such conflicting signals.

The lower arc of the limbic lobe is originally a part of the smell brain, the rhinal cortex, and is therefore called the perirhinal cortex, ('peri-' means 'around' and 'rhinal' means 'nose'). Recall that we stated earlier that not all cortex has six layers; only the giant mammalian cortex does, which is why it is called 'neocortex' (new cortex, because it only emerged 200 million years ago). Older regions of cortex are also found in reptiles, like salamanders, for example, such as the limbic cortex. This region has five cortical layers and is sometimes referred to as 'paleocortex'. It is often associated with emotion and memory and, in the case of the upper arc of the limbic region, with decision-making and the resolution of competing impulses. In addition, the limbic cortex flows continuously into the hippocampus and amygdala, which are hidden inside the temporal lobe, and therefore invisible from the medial perspective. Recent research shows very close interaction between these ancient regions of cortex and episodic memory, i.e. memory for conscious experiences. This is the ancient reptilian brain, which is, however, still a vital center of activity in humans and other mammals.

3.4 The massive interconnectivity of the cortex and thalamus

While the lobes may be thought of as the continents of the brain, their processes are nonetheless intricately intertwined not only with each other, but also with the satellites of the subcortex in the massively interconnected brain.

Sprouting from the cells in the grayish layers of cortex are billions of axons, the output fibers from nerve cells, and dendrites, which provide electrical input to each cell. When white support cells, called the myelin, wrap around those fibers, they look like a white mass to the naked eye, and are therefore called the white matter. The whole giant structure of the cortex is shaped much like a superdome stadium, with two giant halves, each filled with billions of cables going in all directions, centered on a thalamic hub nestled in the middle of each hemisphere (Figure 5.37). The two cortical half-domes, with a thalamic traffic hub on each side, create an extraordinary biological structure. Think of the thalamus as a relay station: almost all input stops off at the thalamus on the way to cortex; almost all output also stops off at the thalamus, going out to the muscles and glands.

Fibers emanating from cortical cells spread in every direction, flowing horizontally to neighboring cells, hanging in great bundles on their way to distant regions of cortex, and converging downward on the great traffic hub, the thalamus, of each half of the cortex. In addition, hundreds of millions of axons flow crosswise, from one hemisphere to the other, creating white axon bridges called commissures (Figure 5.38). The largest crosswise fiber bridge is called the corpus callosum, or 'calloused body'. When the brain is sliced straight through the midline, you can see the corpus callosum as a curved white bow shape. The white color, again, comes from the myelin surrounding the cortical axons that form the great bridge connecting the two hemispheres.

Finally, cortical sensory and motor pathways make up the incoming and outgoing highways of the brain (Figure 5.39). All of these pathways flow from the bottom of the brain. The sensory and motor pathways can be divided into two sets. One set of pathways emerge through small holes in the cranium, the upper skull, and are therefore called the cranial nerves. These include the optic nerve from the back of the eyes, the auditory, olfactory, and taste nerves, as well as the feelings of touch and pain from the face and oral cavity; on the motor side, our facial expressions, vocal apparatus, and mouth, tongue, and so on are also controlled by cranial nerves. The second set of pathways flows into the spinal cord, and controls all our bodily functions, both voluntary – like movements of the torso, arms and legs – and vegetative (autonomic), like blood pressure and sweating.

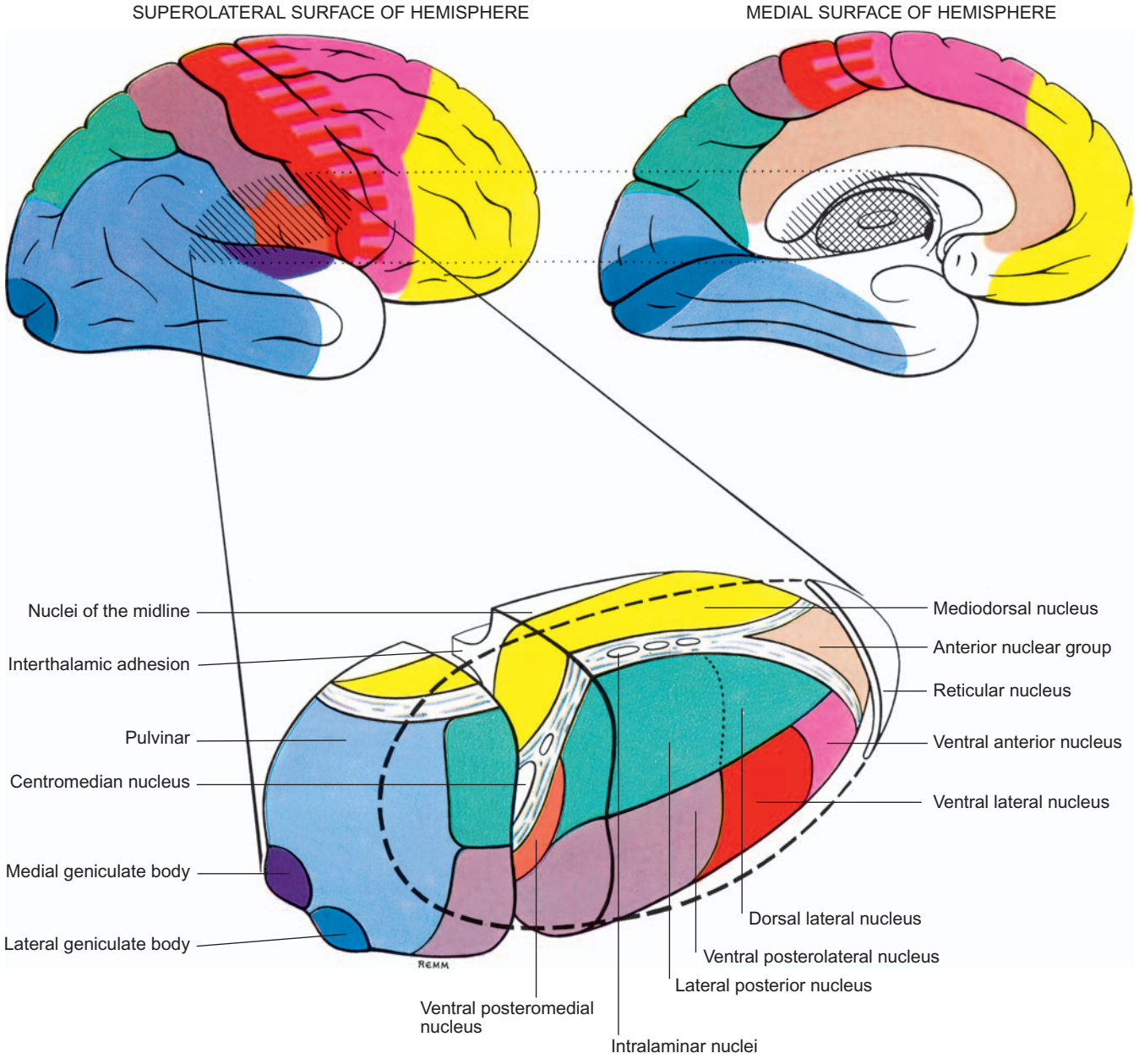


FIGURE 5.37 Cortex and thalamus: a single unified system. A schematic drawing showing a color-coded mapping of connections from the thalamus to cortical regions. *Source*: Standring, 2005.

On the input side, sensory nerves from the body give us all the information, both conscious and unconscious, that we receive from the body. While these pathways are complex in detail, the overview is straightforward.

It is conventional to put an '-o-' between the names of brain regions that are connected, so that we can speak of the 'thalam-o-cortical' connections. Signal flow from cortex to thalamus is called corticothalamic, and, believe it or not, neuronal traffic can even be cortico-thalamo-cortical. It's a little less complicated if you think about it as the traffic flow in a city, or even as the World Wide Web, connecting millions of computers by way of major hubs and pathways.)

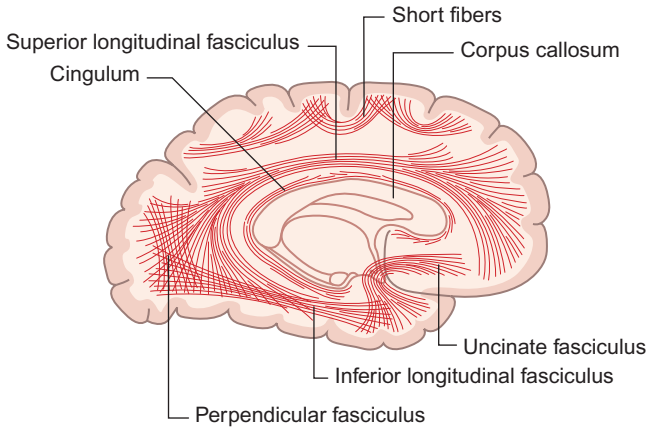


FIGURE 5.38 Schematic drawing of the connectivity of the brain, showing major fiber patterns. *Source*: Standring, 2005.

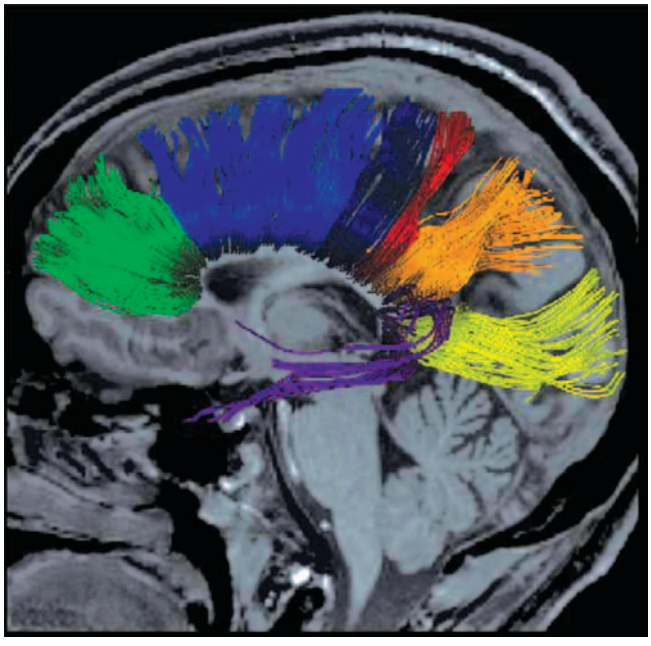


FIGURE 5.39 White bundles of myelinated axons run in all directions through the cortical domes. *Source*: Mario Lazar, with kind permission.

3.5 The satellites of the subcortex

Because the human cortex is so large, it covers important subcortical organs, which act as satellites to the cortex, constantly interacting with it. These subcortical structures don't look like the popular idea of a brain at all – they are giant clusters of neurons often called 'ganglia' or 'nuclei'. Subcortical organs often have remarkably elegant shapes, like loops, horns, and egg-like ovals.

The satellite regions are especially important in cognitive neuroscience. The thalamus, often called the gateway to cortex, was described above; the two thalami reside at the very center of the brain, on both sides of the midline (so you can't actually see them in the medial view). The thalami also connect differing cortical regions, so there are important cortico-thalamo-cortical circuits that have been shown to play a role in attentional processing and other higher order cognition functions. The thalami are nestled above the brainstem and just below cortex, a perfect location to serve their role as the relay station for the brain.

The *hippocampal complex* (see Figure 5.17) is critical to remembering conscious experiences, and appears as two small sausages embedded in each temporal cortex. However, it is now known that areas adjacent to the 'sausage' of hippocampus are also needed for episodic (experiential) memory. For that reason we will talk about the entire hippocampal complex, rather than just the hippocampus alone.

At the very front tip of each hippocampus is the *amygdala*, Latin for 'almond' (see Figure 5.18). It has a small spherical nut-like shape, profoundly important for emotions like fear and anger, as well as learning processes that involve those emotions. Finally, the *basal ganglia* (see Figure 5.19) are complex disk-and-loop structures just outside of each thalamus, and the *cerebellum* (or little brain) rides on the back of the entire upper brainstem and thalami. The basal ganglia have been implicated in action planning and unconscious cognitive operations. New evidence, however, has linked the basal ganglia to higher order cognitive functions, such as decoding the grammar, or syntax, of language.

The cerebellum is seated on the rear of the lower brainstem. It is itself a very large structure. In many mammals, the cerebellum has as many neurons as the cortex itself, though they have shorter axons. Most cerebellar neurons are connected locally, in small clusters. Historically, the cerebellum was thought to be mainly involved in controlling fine motor movements, like the finger movements of a typist or musician. It is now also known to be necessary for cognitive functions as well. Indeed, functional imaging shows the cerebellum to 'light up' in almost any cognitive task. The reason for this is not completely understood.

Finally, a number of tiny nuclei of the brainstem and basal forebrain send cell fibers widely through the upper brain. These neuromodulating nuclei are sometimes informally called 'spritzers', because they

spray neurochemicals from their axon terminals so that those chemicals are widely dispersed. Spritzers may contain only a few thousand neurons, but they are crucial to a healthy brain. Major disorders like Parkinson's disease, characterized by disabling motor tremor, result from defects of such neuromodulators. They also control the daily sleep-waking cycle.

We end this section with a description of the reticular formation, located at a central point in the brain (Figure 5.40). This is a particularly intriguing area of the brain in terms of its role in human conscious experience. The reticular formation is called 'reticular' (i.e. network-like) because the neuronal axons in this system are usually very short, suggesting a great amount of interaction between adjacent neurons. Further, it receives input from all sensory and motor systems, as well as from other major structures in the brain. Through its connections with the thalamus, it can send information to, and receive it from, all areas of the cortex.

What does this suggest about the role of the reticular formation in conscious experience? There is neurophysiological evidence that specialist systems in the brain can cooperate and compete for access to a central integrative 'blackboard'. There is reason to think that the *extended reticular-thalamic system* (ERTAS) corresponds to this 'blackboard'.

This is not a new notion; Aristotle's 'common sense' was supposed to be a domain of integration between the different senses. In fact, anatomists who have studied the reticular formation have pointed to its resemblance to Aristotle's concept. Scheibel and Scheibel (1965) point out that 'Anatomical studies of Kohnstamm and Quensel, which suggested pooling of a number of afferent and efferent systems upon the reticular core, led them to propose this area as a "centrum receptorium 2" or "sensorium commune" – a common sensory pool for the neuraxis'.

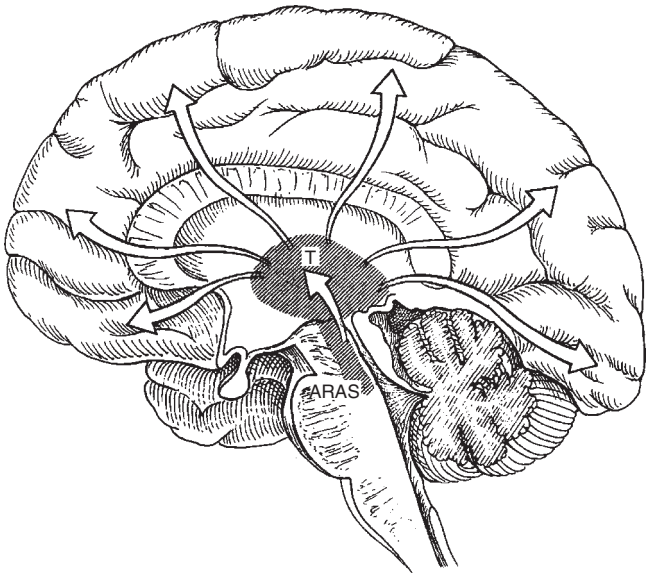


FIGURE 5.40 The ascending reticular activating system (ARAS) is found in the brainstem and thalamus, and sends projections throughout cortex. The ARAS is thought to be required for the normal conscious waking state. *Source*: Filley, 2002.

Moreover, these authors note that '. . . the reticular core mediates specific delimitation of the focus of consciousness with concordant suppression of those sensory inputs that have been temporarily relegated to a sensory role' (p. 579). Along similar lines, Gastaut (1958) describes the brainstem reticular formation as an area of 'convergence . . . where signals are concentrated before being redistributed in a divergent way to the cortex'. Thus, different sensory contents can suppress each other, as we would indeed expect of input to a global workspace. This suggests that different specialized processors can compete for access to the ERTAS.

How does this 'blackboard' concept actually work in terms of neural processes and how are messages broadcast? In one possible scenario, one sensory projection area of the cortex provides input to the ERTAS. If this input prevails over competing inputs, it becomes a global message which is widely distributed to other areas of the brain, including the rest of the cortex. Thus, one selected input to the ERTAS is amplified and broadcast at the expense of others. Thus, in this way, the ERTAS underlies the 'global broadcasting' function of consciousness, while a selected perceptual 'processor' in the cortex supplies the particular contents of consciousness which are to be broadcast.

What is the role of the ERTAS in conscious thought? It may be the case that any cortical activity must trigger ERTAS 'support' in a circulating flow of information, before it can be broadcast globally and become conscious (e.g. Scheibel and Scheibel, 1965; Shevrin and Dickman, 1980). Dixon (1971) has also argued that a circulating flow of information between the reticular formation and the sensory areas of the cortex is required before sensory input becomes conscious.

The possible role of the ERTAS in conscious experience is an intriguing one! It makes intuitive sense that there must be some kind of broadcast system in the brain that allows for all modes of sensory processing – sight, hearing, touch – to combine with conscious thought and experience in order to focus on some inputs and suppress others. Clearly, the ERTAS does

not work in isolation in these types of brain functions. The thalami and regions in the prefrontal cortex are likely closely intertwined with ERTAS-like processes. Nevertheless, ERTAS seems to play a key role in human conscious experience.

4.0 SUMMARY

It is a difficult task indeed to attempt to describe a dynamic and complex biological structure such as the brain in a few short pages. Our aim in this chapter was to provide you with the basic structures and regions of the brain and their function in human cognition. Some important points to remember are that the brain has developed and changed through time and so some areas of the brain are 'older' than others. The cortex or neocortex represents recent brain developments in the human, and the frontal and parietal lobes have expanded their neural territory tremendously as compared to non-human primates. While there are separable regions and parts of the brain, such as the two hemispheres and the four major lobes, nonetheless, the brain is highly interconnected with an extensive fiber pathway system that connects the hemispheres, the lobes, and provides circuits to subcortical regions.

Some important questions about human brain structure and function remain a puzzle to us. Why do we see so much evidence of duality in the brain, with two hemispheres, two thalami, for example, when we have one mind? What role do the mirror image regions of the brain play in human cognition? While some 'newer' regions of the brain, such as the prefrontal cortex and the inferior parietal lobe, seem to be the site for higher order associative cognition, there are also some ancient regions, such as the reticular formation, that seem to play a key role in consciousness. New and ancient, the many regions of the brain come together to form a dynamic and intricate biological structure that holds many more puzzles for scientists to unravel.

5.0 CHAPTER REVIEW

5.1 Study questions

1 Why is cortex sometimes referred to as 'neocortex'?
2 What are the four major lobes of the brain and what are some of their key functions in human cognition?
3 Where is the medial temporal lobe located? What are its key structures?
4 Briefly describe the role of the thalami in brain processing.
5 How are the hemispheres linked? Are there any differences in how they function?
6 What is the reticular formation and what role may it play in conscious thought?

5.2 Drawing exercises

Show the locations and names of the major brain landmarks using Figure 5.41 on page 156.

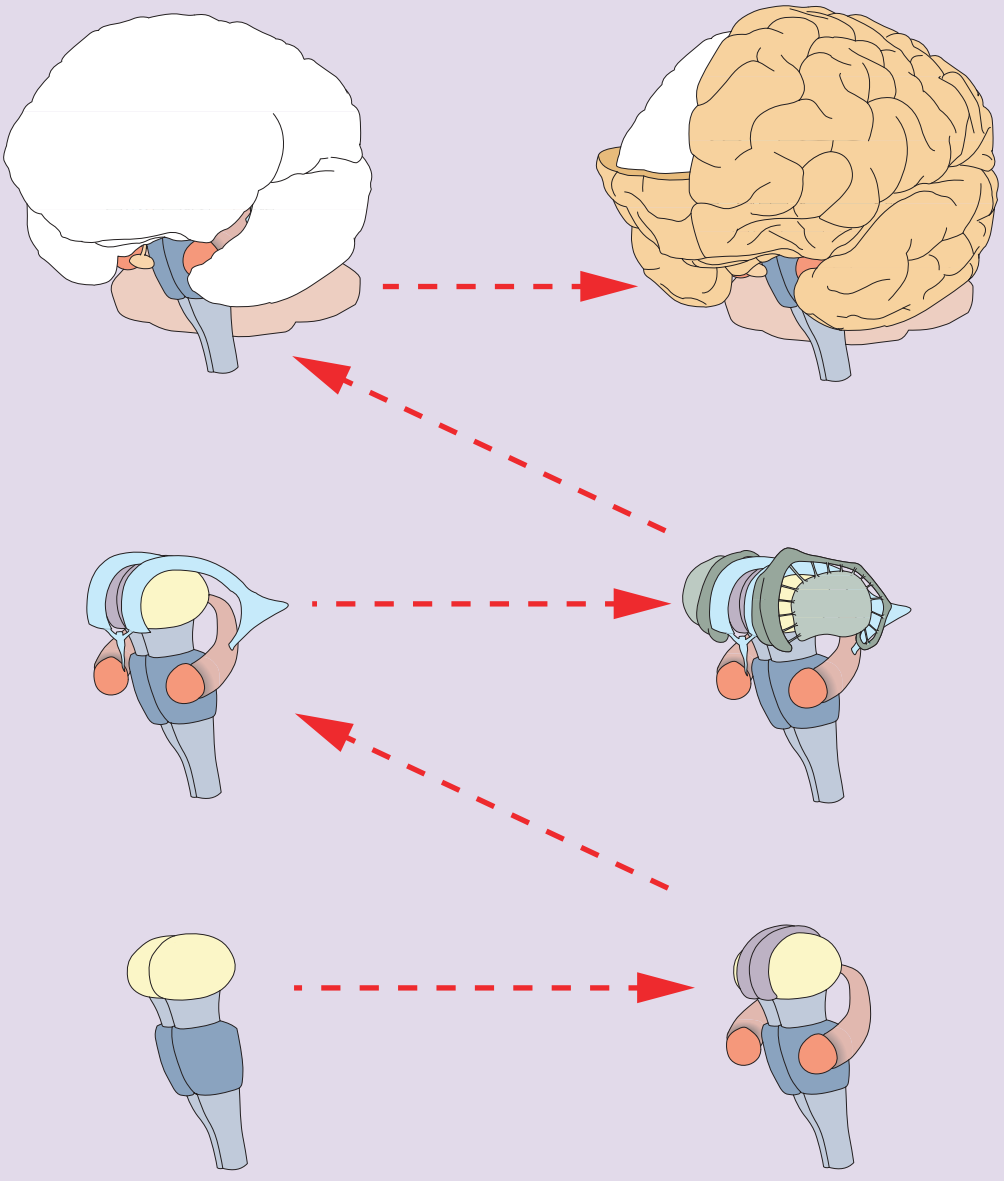


FIGURE 5.41 Building the brain figure for the Drawing Exercise.

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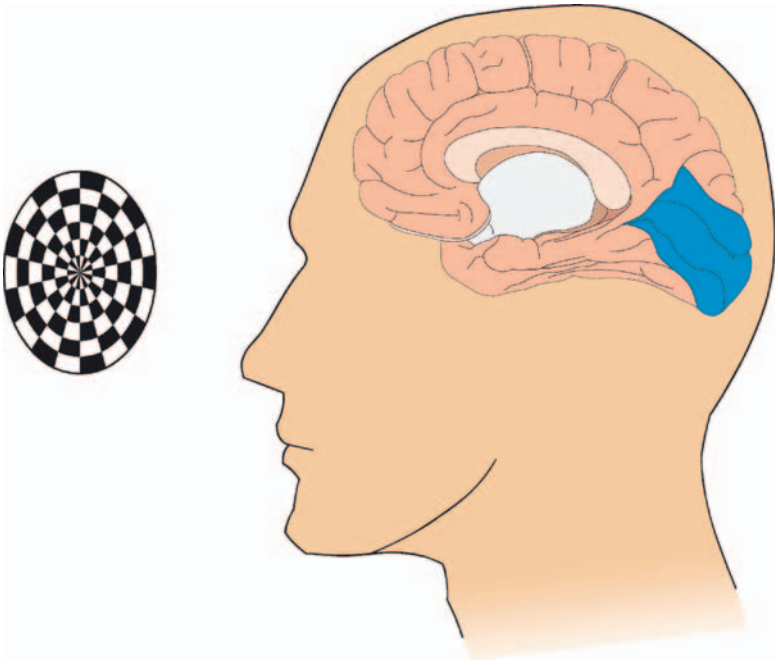
The question is not what you look at, but what you see.

Henry David Thoreau



An abstract figure showing a rotating checkerboard stimulus, which highly activates the early visual areas located in the occipital lobe (in blue). Notice that we are looking at a medial view of the right hemisphere. *Source*: Buckley and Gaffan, 2006.

CHAPTER

6

Vision

OUTLINE

1.0 INTRODUCTION

1.1 The mystery of visual experience

Think back to the last time you stood aloft a high lookout, looking down at the world below. Perhaps you were at the top of a summit and could see the wide expanse of the horizon cut by repeating mountaintops, forests, valleys, and rivers below, or perhaps you were at the top of a tall building as the bustling swirling colors of rush-hour traffic, cars, and people flowed through the streets. It's worth pausing for a moment to think about how such vivid and powerful impressions can be the simple result of a collection of neurons firing

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

inside your brain. How can the collective electrical activity of billions of neurons be responsible for everything you are seeing and experiencing at this very moment? These are some of the perplexing but fascinating questions that arise when we consider the relationship between brain activity and subjective visual experience.

Most people intuitively think that human vision works much like a camera (Figure 6.1(a)). As we go about our daily activities, it is easy to believe that we see our entire world in crisp full-resolution color – much like a high-resolution photograph. However, as it turns out, this is far from the case. Due partly to the structure of our eyes (which we will revisit shortly), our visual perception is in full color and high resolution only at the center of gaze. This may seem hard to believe, as you dart your eyes around the room now; the illusion that you are experiencing the whole visual scene in full color and clarity seems convincing. However, if you fix your gaze at a particular point in space – say the corner of the windowsill or this word on the page – and get someone to hold up some fingers out at the edge of your field of view, you will find that without moving your eyes it is extremely hard to count the number of fingers he or she holds up. Also, you may notice that your experience of color is somehow dull and lacking in richness.

There are several reasons why it makes sense to restrict high-resolution vision to only a small portion of our visual space – this is just one of the many strategies that the brain uses to help represent the specific features and objects we see in the most efficient and effective way possible. It is a testament to the brain's ability seamlessly to represent the outside world that we normally remain oblivious to this striking fact.

1.2 The purpose of vision: knowing what is where

For most people, vision may be the most important of the five senses for getting around in everyday life and getting things done. What is the purpose of vision? David Marr, an early vision scientist and computer expert, made the deceptively simple comment that the goal of vision is '*to know what is where*'. For example, if you are walking or driving to the university to find a class in a new building, it is important to know: *where are the other cars and pedestrians, is the light red or green, which way is that car going, how fast is it approaching, do I turn at this street corner, is this the building I'm looking for*?

Considering the goal of vision, it becomes clear that visual perception is far more complicated than simply taking a picture with a digital camera (Figure 6.1(a)). A digital camera can capture the image projected from the environment and store it in an array of pixels. However, the camera doesn't really do anything with this image and doesn't have any knowledge about what is stored in the image, such as what objects are in the photo or where

(a) (b)

FIGURE 6.1 Visual experiences. (a) Just one of millions of images you can experience with your visual system. Unlike the camera, you actually experience the image; you know what it is you are looking at. (Image courtesy of the Tong lab.) (b) Another example of the detailed, multifeature capabilities of your visual system. You can differentiate many different orientations, colors, and shapes. *Source*: Frank Tong, with permission.

they are. The easiest way to figure out what is in the picture is to have someone look at the picture and interpret it with his or her brain. Visual perception is what happens *after* the picture reaches the eyes – the image forms a pattern of activity on the array of receptors in the eye, and the detailed pattern is analyzed by the visual centers of the brain, thereby revealing what is where.

1.3 Knowing what: perceiving features, groups, and objects

How does the brain perceive what something is? Studies of human visual perception and neuroscience suggest that there are many levels of perception. At the most basic level, the human brain appears to process basic *visual features* such as *color*, *orientation*, *motion*, *texture*, and *stereoscopic depth*. For example, when looking at the picture of the flower shown in Figure 6.1(b), we may perceive that the center of the flower is yellow, the leaf just below is green, and the two stems are each at different angles. We are very good at perceiving small differences in orientation (1–2 degrees of angular tilt), subtle differences in color (e.g. the red of a rose or the red of a strawberry), and very faint traces of motion.

As we will see in the next section, most neurons in early visual areas of the brain are highly tuned to specific features – some may fire very strongly to a line shown at a particular angle, to a particular color, or to a particular motion direction. These neurons respond to a very small region of the visual field (i.e. your current field of view), ranging from just a fraction of a degree to a few degrees of visual angle. (If you hold your thumb at arm's length, the width of your thumb is probably about two degrees of visual angle (O'Shea, 1991). (The moon, when viewed from Earth, is about 0.5 degrees in diameter.)

If the activity of each of these neurons represents only a small part of the visual field, such as whether a small patch of the visual field contains vertical or horizontal, red or blue, motion or something stationary, then how is the brain able to combine this information across many neurons? Somehow, the brain is able to organize these basic feature elements into organized *perceptual groups*. The *Gestalt* psychologists proposed that perception could not be understood by simply studying the basic elements of perception (Wertheimer, 1912; Koffka, 1935). The German word, *Gestalt*, is difficult to translate directly, but expresses the idea that *the whole is greater than the sum of the parts*. These psychologists proposed the *Gestalt laws of perceptual grouping*, such as the laws of *similarity*, *proximity*, *good continuation*, *common fate*, and so forth (Figure 6.2). These laws suggest that elements more similar in color or shape are more likely to be perceived as a group. Likewise, if a set of elements is arranged in a way that they are more closely spaced in rows or columns, this will determine whether they are perceived as rows or columns.

Why is perceptual grouping so important? It helps us perceive which features belong to a possible object,

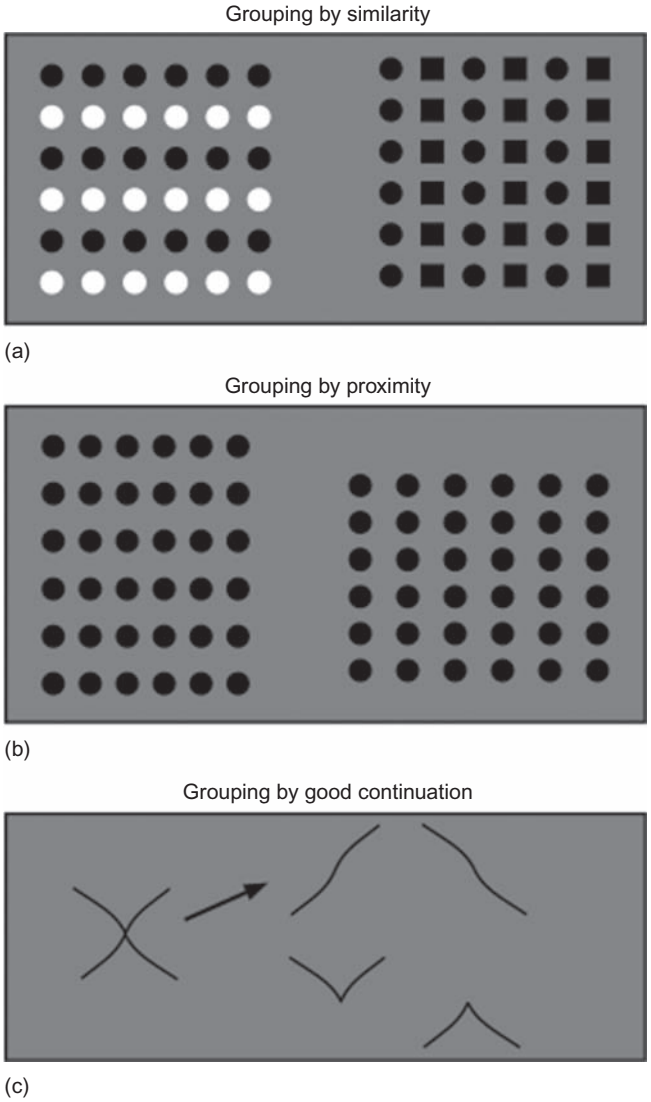


FIGURE 6.2 Gestalt grouping. (a) Grouping by similarity, the white dots are grouped with other white dots. On the right, the squares group with squares. The objects with similar features tend to group together. (b) Here, even though all the objects are circles, due to their grouped locations or proximity to each other, we perceive two separate groups of dots. (c) Grouping by good continuation. On the left, we perceive one object. On the right, the exact same lines are drawn but separated so that there is no continuation across the entire object. In all these cases, the collections of objects form groups or larger global objects, which are greater than the simple sum of the parts. *Source*: Frank Tong, with permission.

and helps us distinguish an object from the background. For example, imagine seeing a golden retriever lying in tall grass. Grouping by similarity may help us see that the dog is separate from the grass, and the neighboring wagging tail might be recognized as part of the dog, even though only the end of the tail can be seen. If the dog starts to run toward a bush, barking furiously, the cat hidden behind the bush may be invisible until it starts to move, because the cat's motion leads to grouping by common fate, which may evoke a vivid impression of the complete shape of the animal rather than bits and fragments of fur separated by branches and leaves.

Finally, we can perceive the shape of entire *objects*, and match these shape representations to the objects we know from previous experience. To perceive an object, the brain has to go through many stages of visual processing, from processing the feature elements of the object, putting the elements together into coherent groups, and finally figuring out how those elements form a coherent organized shape. This representation of the object's shape must then be matched to the correct object representation stored in memory. Given that there are thousands of objects and that the two-dimensional image of any object projected onto the back of the eye can vary from changes in viewpoint, lighting, or viewing conditions, this makes the problem of object recognition especially challenging. Somehow, the brain must abstract the stable or invariant properties of an object while disregarding all the superficial ways in which the 2D image of an object can vary.

Later in this chapter, we will discuss how the brain processes different types of visual features and objects.

1.4 Knowing where things are

How do we know where objects are located in the world? When we look at the world, the image that strikes the back of our eye is essentially two-dimensional, similar to the image that would be taken by a camera. This two-dimensional map of the world projected onto the eye is preserved in the early visual areas of the cerebral cortex, which provides a map of where objects are located relative to the center of gaze. The brain is also able to figure out the missing third dimension and estimate how far away objects are in space. Whereas early visual areas represent the positions of objects relative to the center of gaze, higher brain areas in the parietal, temporal, or frontal lobe are more likely to represent the position of objects in a more abstract (less visual) manner, relative to the person's body position or relative to the global environment.

2.0 FUNCTIONAL ORGANIZATION OF THE VISUAL SYSTEM

When the light coming from an object reaches our eyes, it triggers a cascade of neural events as this visual pattern is converted into neural impulses that travel up the visual system, from one brain area to the next. Through a series of neural processes in many brain areas, the activity of neurons in numerous brain areas somehow leads to the visual experience and recognition of the object and its many component features. Let's trace the sequence of events to understand how the brain processes visual information at each stage of visual processing. This will help us understand how different visual areas of the brain contribute to visual perception.

2.1 The retina

There are two types of photoreceptors: *cones* and *rods* (Figure 6.3). Cones are color-selective, less sensitive to dim light than rods, and important for detailed color vision in daylight. Each cone contains one of three kinds of *photopigments*, specialized proteins that are sensitive to different wavelengths of light. These wavelengths roughly correspond to our ability to distinguish red, green, and blue. When light strikes a photopigment molecule, the light energy is absorbed and the molecule then changes shape in a way that modifies the flow of electrical current in that photoreceptor neuron. Cones are densely packed into the *fovea*, the central part of the retina that we use to look directly at objects to perceive their fine details. In the periphery, cones are more spread out and scattered, which is why objects in the periphery appear blurrier and their colors are less vivid.

Rods contain a different photopigment that is much more sensitive to low levels of light. Rods are important for *night vision* – we rely on seeing with our rods once our eyes have adapted to the darkness (*dark adaptation*). Curiously, there are no rods in the fovea, only cones, and the proportion of rods increases in the periphery. This is why you may have noticed when gazing at the night sky that a very faint star may be easier to see if you look slightly off to one side.

The signals from photoreceptors are processed by a collection of intermediary neurons, *bipolar cells*, *horizontal cells*, and *amacrine cells*, before they reach the *ganglion cells*, the final processing stage in the retina before signals leave the eye. The actual cell bodies of ganglion cells are located in the retina, but these cells have long axons that leave the retina at the *blind spot* and form the *optic nerve*. Each ganglion cell receives excitatory

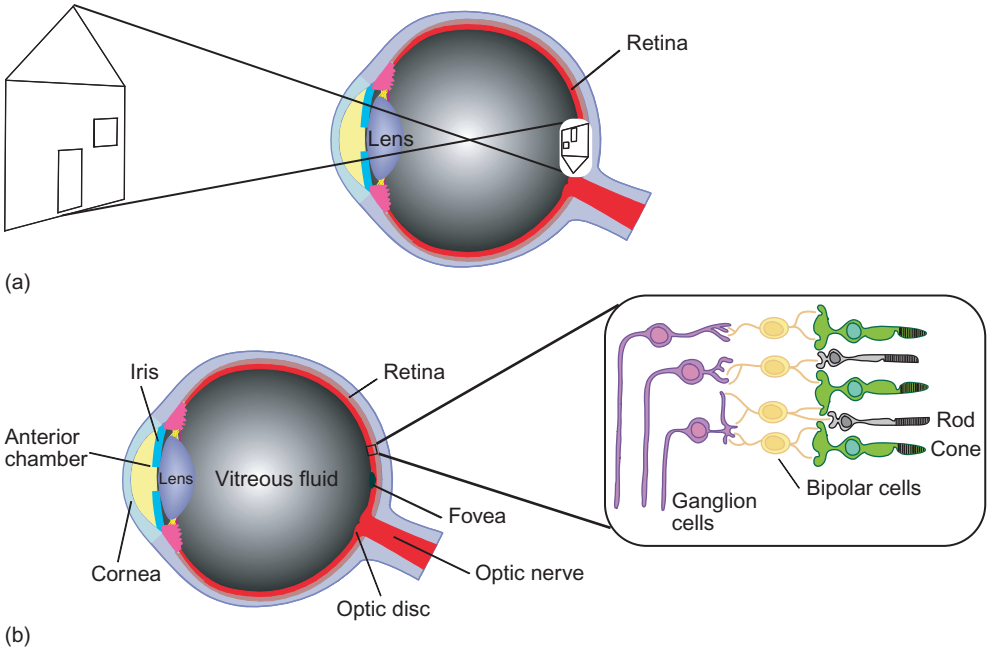


FIGURE 6.3 The eye. (a) Illustration showing how objects in the environment are physically projected to the back of the eye – the retina. (b) The eye and a cross-section of the retina. The cross-section of the eye shows where the photoreceptors are located in the retina. Both the rods and cones are shown. They respond to different types of light. The neural signal then travels via bipolar cells and then to the ganglion cells. The axons of the ganglion cells take the neural information out of the eye and backward toward the cortex. *Source*: Squire *et al.*, 2003.

inputs from a collection of rods and cones – this distillation of information forms a *receptive field* – a concept we will revisit shortly. Ganglion cells at the fovea receive information from only a small number of cones, while ganglion cells in the periphery receive inputs from many rods (sometimes thousands). With so many rods providing converging input to a single ganglion cell, if any one of these rods is activated by photons of light, this may activate the cell, which increases the likelihood of being able to detect dim scattered light. However, this increase in sensitivity to dim light is achieved at the cost of poorer resolution – rods provide more sensitivity, but also a 'blurrier' picture than the sharp daytime image provided by cone vision.

Retinal ganglion cells receive both excitatory and inhibitory inputs from bipolar neurons, and the spatial pattern of these inputs determines the cell's *receptive field* (Figure 6.4(a)). A neuron's receptive field refers to the portion of the visual field that can activate or strongly inhibit the response of that cell. Retinal ganglion neurons have center-surround receptive fields. For example, a cell with an *on-center off-surround* receptive field will respond strongly if a spot of light is presented at the center of the receptive field. As that spot of light is enlarged, responses will increase up to the point where light begins to spread beyond the boundaries of the on-center region. After that, the response of the ganglion cell starts to decline as the spot of light gets bigger and stimulates more and more of the surrounding off-region. (A cell with an off-center on-surround receptive field will respond best to a dark spot presented in the center of the receptive field.)

How can the behavior of retinal ganglion cells be understood? A key concept is that of *lateral inhibition* (Kuffler, 1953). Lateral inhibition means that the activity of a neuron may be inhibited by inputs coming from neurons that respond to neighboring regions of the visual field. For example, the retinal ganglion cell in Figure 6.4(b) receives excitatory inputs from cells corresponding to the on-center region, and inhibitory inputs from the off-center region. The strength of these excitatory and inhibitory inputs are usually balanced, so that if uniform light is presented across both on- and off-regions, the neuron will not respond to uniform illumination.

Why are center-surround receptive fields and lateral inhibition so important? Lateral inhibition is important for enhancing the neural representation of *edges*, regions of an image where the light intensity sharply changes. These sudden changes indicate the presence of possible contours, features, shapes, or objects in any

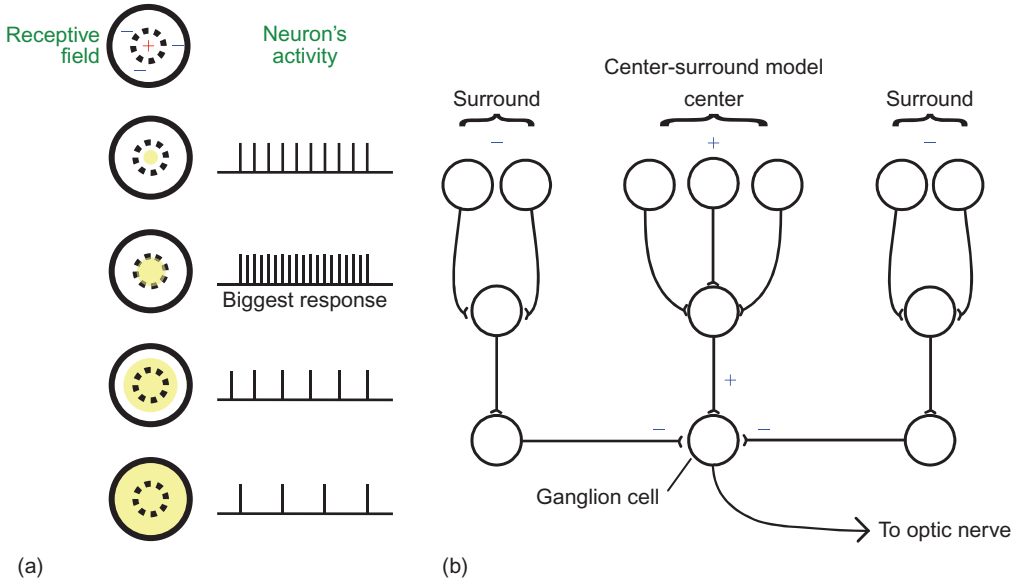


FIGURE 6.4 Center-surround receptive fields. (a) Schematic example of a center-surround cell's response to different-sized patches of light. Notice that the biggest spiking response (shown by the lines on the right) occurs for the intermediate-sized center light patch. The spot of light has to be just the right size to get the maximum response out of that particular neuron. (b) A model of how a center-surround receptive field might be achieved by the collaboration and competition between different connective neurons in the retina. *Source*: Frank Tong, with permission.

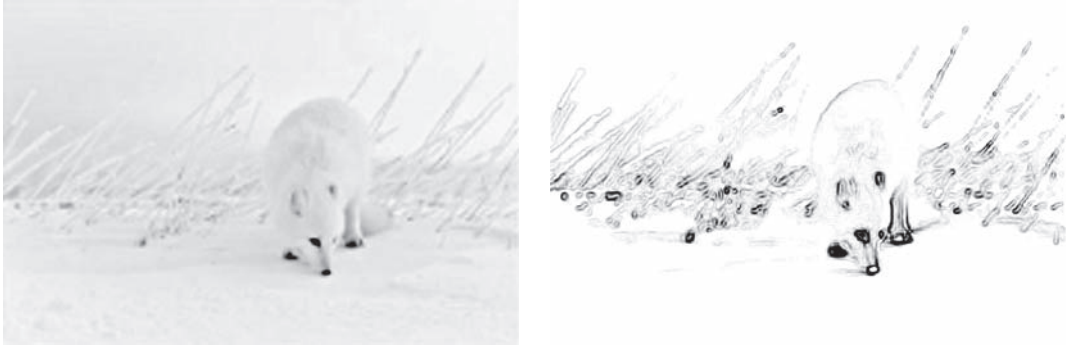


FIGURE 6.5 The edges hold most information. An example of how most of the information in the picture comes from the edges of objects. Figure on the left is the original, on the right is information from the edges only – taken from the image using a computer algorithm. *Source*: Frank Tong, with permission.

visual scene, whereas uniform parts of a picture are not particularly informative or interesting. Figure 6.5 shows a picture of the fox in original form and after using a computer to filter out just the edges (right picture), so that the regions in black show where ganglion cells would respond most strongly to the image. Lateral inhibition also leads to more efficient neural representation, because only the neurons corresponding to the edge of a stimulus will fire strongly; other neurons with receptive fields that lie in a uniform region do not. Because the firing of neurons takes of a lot of *metabolic energy*, this is much more efficient. This is an example of *efficient neural coding* – only a small number of neurons need to be active at any time to represent a particular visual stimulus.

Lateral inhibition also helps ensure that the brain responds in a similar way to an object or a visual scene on a dim gray day and on a bright day. Changes in the absolute level of brightness won't affect the pattern of activity on the retina very much at all; it is the relative brightness of objects that matters most. Finally, lateral inhibition at multiple levels of visual processing, including the retina, lateral geniculate nucleus (LGN), and visual cortex, may lead to interesting visual illusions such as the Hermann grid illusion (Figure 6.6).

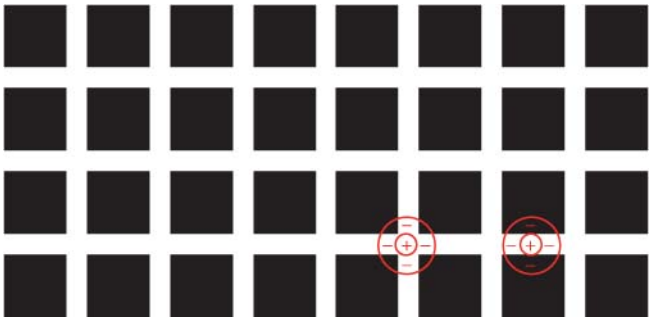


FIGURE 6.6 Hermann grid illusion. Take a careful look at the collection of black squares in the figure. Do you notice anything unusual? Do you have the impression of seeing small dark circles in between the black squares in the periphery? Don't be alarmed, this is completely normal. This is a great example of receptive fields with lateral inhibition at work (Herman, 1870). In the rightmost matrix of squares, some possible receptive fields are shown. A receptive field that falls between the corners of four dark squares will have more of its inhibitory surround stimulated by the white parts of the grid than a receptive field that lies between just two of the dark squares. As a result, neurons with receptive fields positioned between four dark squares will fire more weakly, leading to the impression of small dark patches at these cross points. At the fovea, receptive fields are much smaller so the illusion is only seen in the periphery. *Source*: Frank Tong, with permission.

2.2 Lateral geniculate nucleus (LGN)

From the eye, retinal ganglion cells send their axons to a structure in the thalamus called the *lateral geniculate nucleus* (LGN). Specifically, the left half of each retina projects to the left LGN; the right half of the retina projects to the right LGN. For this to happen, the inputs from the nasal portion of each retina must cross at the *optic chiasm* to project to the opposite LGN (Figure 6.7). The result is that the left LGN receives input from the right visual field, and the right LGN receives input from the left visual field, so that each LGN serves to represent the *contralateral* (i.e. opposite) visual field. Note that the inputs from each eye go to separate monocular layers of the LGN, so signals from the two eyes remain separate until they reach the *primary visual cortex* where these signals are combined.

What do the receptive fields in the LGN look like? Well, they share the same shape and basic properties of the retinal ganglion cells with center-surround receptive fields. The thalamus is often considered a way station

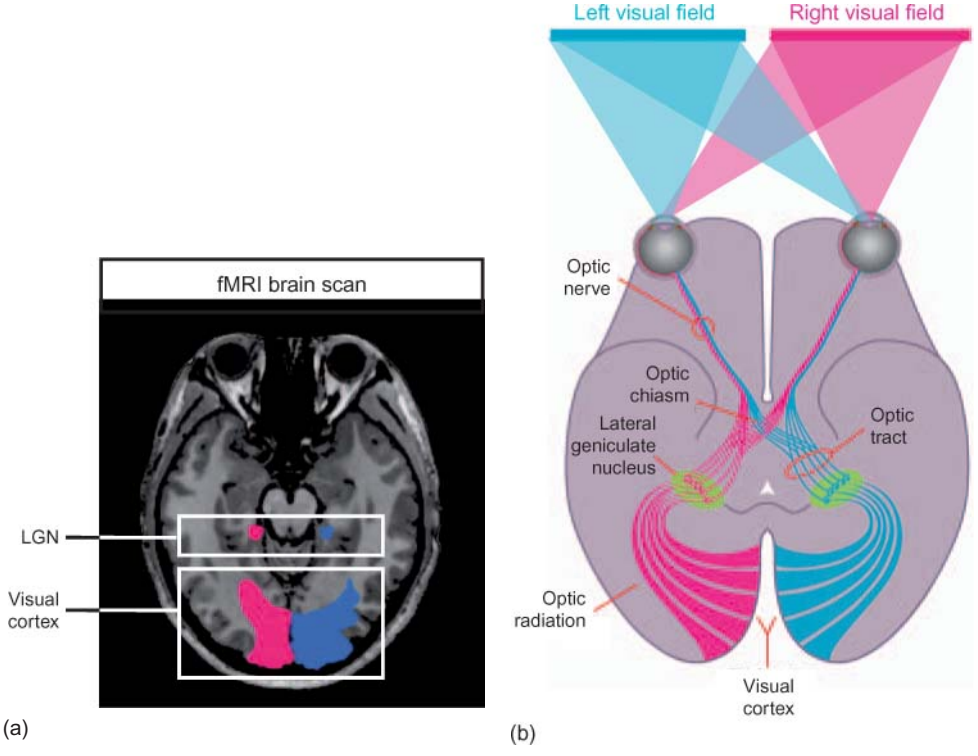


FIGURE 6.7 The visual pathways from retina to cortex. (a) Example of a brain slice from a functional magnetic resonance imaging (fMRI) scan, showing the lateral geniculate nucleus (LGN) and primary visual areas at the back of the brain (the occipital cortex). The two different colors denote the two hemispheres of the brain. (b) Schematic illustration showing the visual pathways from the retina in the eyes to the primary visual cortex at the back of the brain. You can see here that the neural information from the nasal or inner sides of the eyes crosses over at the optic chiasm, to be processed in the contralateral side of the brain. The left visual field, in blue, is processed by the right visual cortex (also blue). The LGN, displayed in green, relays the visual information to the primary visual areas of the cortex. *Source*: Squire *et al.*, 2003.

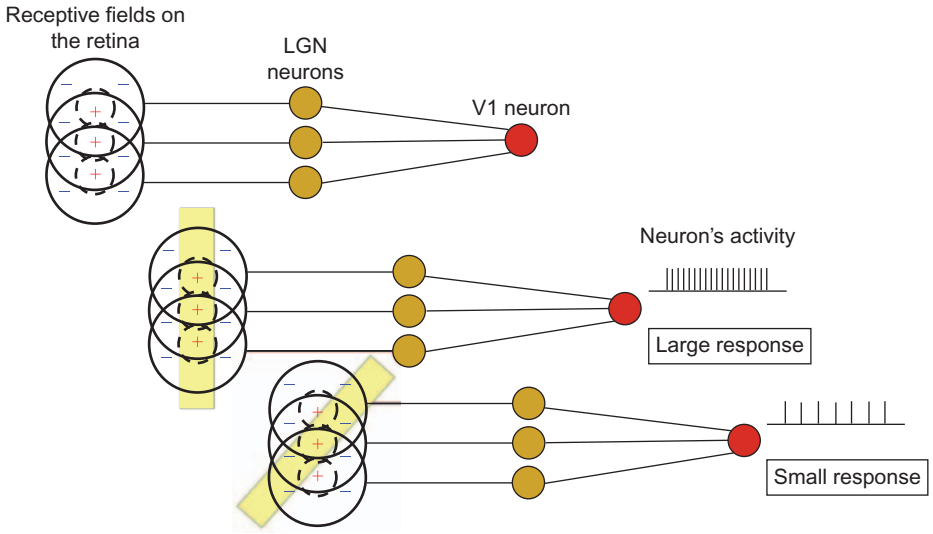


FIGURE 6.8 Orientation selectivity in V1. An example of how a collection of center-surround receptive fields could lead to orientation selectivity in V1 neurons. The overlapping circles on the left show center-surround receptive fields. When the bar of light lays vertically it triggers all the on-centers (+) of each receptive field, whereas when its orientation changes (the bar tilts) fewer centers and more surrounds are activated resulting in a smaller neural response (fewer spike bars in the graph). Hence the vertical bar gives a larger neural response, when the stimulus is oriented the magnitude of the V1 response is reduced. This constitutes orientation selectivity – only observed in the cortex. *Source*: Frank Tong, with permission.

for signals finally to reach the cerebral cortex, where the neurons start to respond in very different ways.

So how would LGN neurons or retinal ganglion cells respond to the simple outline of the house, as is illustrated in Figure 6.10? Cells with on-center receptive fields positioned on any of the contours of the house would fire strongly. Note, though, that these cells will fire just as strongly for a vertical, horizontal, or tilted line. Although a small portion of the inhibitory surround is stimulated by these lines, the entire proportion of the on-center region is being stimulated, leading to greater excitation than inhibition, and therefore a steady level of firing.

2.3 Primary – or striate – visual cortex (V1)

From the LGN, neurons send their signals to the primary visual cortex, sometimes called *V1* because this region is the first cortical visual area. *V1* is frequently referred to as 'striate' cortex because of its distinguishing striped – or striate – appearance. About 90 percent of the outputs from the retina project first to the LGN and then onward to V1. The left LGN projects to V1 in the left hemisphere; the right LGN projects to right V1 (Figure 6.7). In V1, the spatial layout of inputs from the retina is still preserved. Left V1 receives an orderly set of inputs from the left half of both retinas, via the thalamus. The foveal part of the visual field is represented in the posterior part of the occipital lobe, near the occipital pole and the more peripheral parts of the visual field are represented more anteriorly. Left V1 therefore contains a *retinotopic map* of the entire right visual field, while right V1 contains a map of the entire left visual field. This retinotopic organization is very prevalent in early visual areas (V1 through V4), where neurons have small receptive fields, but becomes weaker and less orderly in higher visual areas outside of the occipital lobe.

Neurons in V1 are sensitive to a whole host of visual features, not seen in the LGN. One of the most important visual features is *orientation* (Hubel and Wiesel, 1962, 1968). Some V1 neurons respond best to vertical lines, some to 20-degree tilted lines, others to horizontal lines and so forth. How do these neurons attain these new properties or receptive fields? Figure 6.8 shows an example of a model for V1 orientation selectivity. If a V1 neuron receives excitatory input from three LGN neurons with aligned center-surround receptive fields, then the V1 neuron will respond best to a matching oriented line. For example, if a vertical bar is presented, the neuron shown in the figure will respond at its strongest, because the entire excitatory region will be stimulated, whereas the inhibitory surround will not be stimulated. If the bar is tilted somewhat away from vertical, the neuron will respond more weakly because part of the inhibitory surround will now be stimulated and part of the excitatory center will not. Finally, if a horizontal bar is presented, the neuron may not fire at all, because equal proportions of the center and the surround regions will be receiving stimulation, leading to a balance in the strength of incoming excitatory and inhibitory inputs. This configuration of center-surround receptive fields can explain the orientation selectivity of V1 neurons.

V1 neurons are also sensitive to many other *visual features* besides orientation (Hubel and Wiesel, 1998). Some neurons respond best to a particular *direction of motion*, such as upward motion, leftward motion, or downward motion. Other neurons respond best to particular colors or color differences (e.g. red versus green, yellow versus blue), though some basic types of color-sensitive neurons can also be found in the retina and LGN. Finally, some neurons respond best

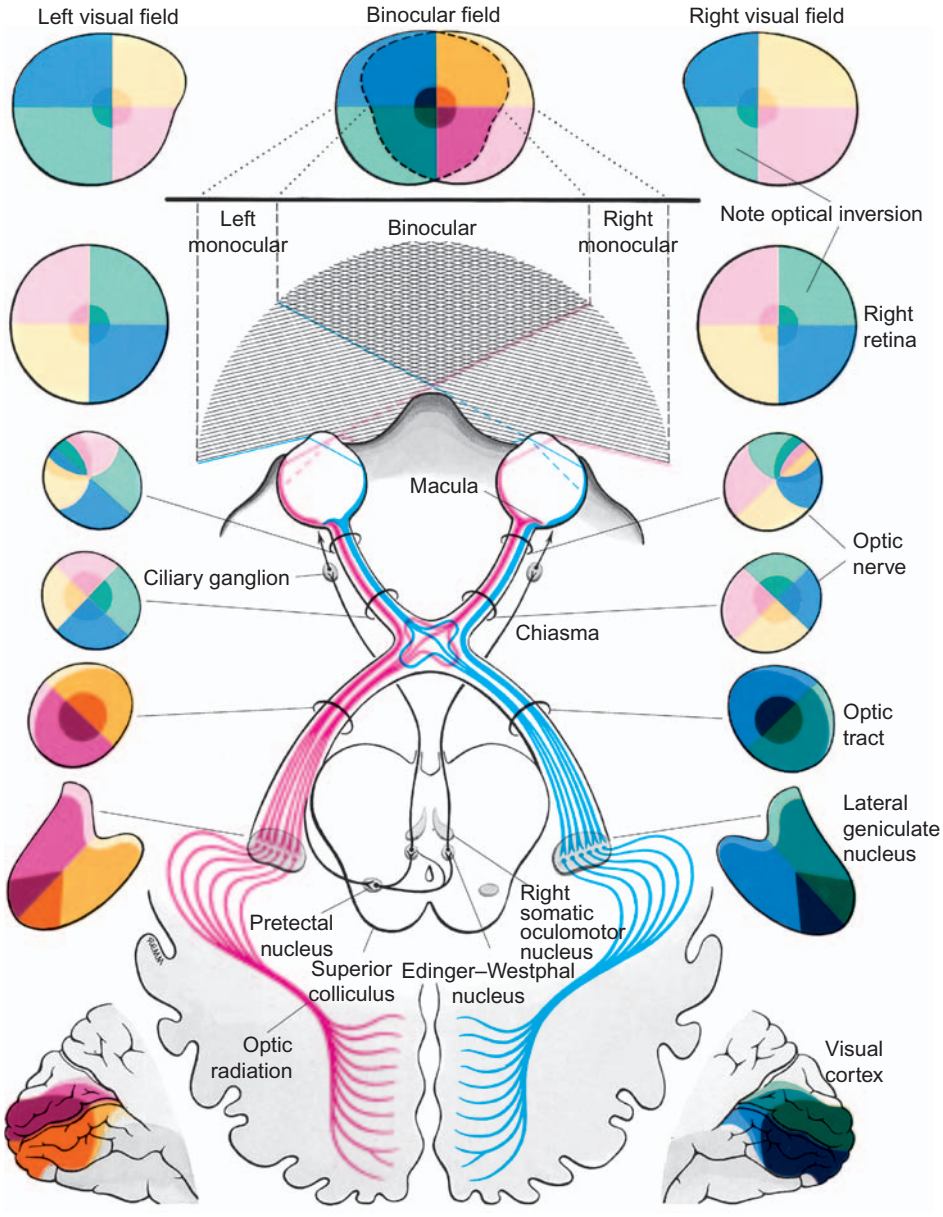


FIGURE 6.9 Pathways in the visual system: from the eye to V1. A schematic drawing of the pathways in binocular vision, showing the visual input from left and right visual fields (top of figure) through the optic nerve and optic tract (center of figure), continuing on through the LGN and onto V1 in cortex (bottom of the figure). *Source*: Standring, 2005.

to particular *binocular disparities* (Barlow *et al.*, 1967; Cumming, 2002), which refer to the degree of alignment between images in the two eyes. Small displacements between images in the two eyes are what allow us to perceive stereo-depth when we look at objects with both eyes open. (Try closing one eye, extending your arms to full length and try quickly to move your two index fingers to meet one another. Now try this again with both eyes open. If you have normal binocular vision, this should be much easier to do with both eyes open because you can better judge the distance of your two fingers.) See Figure 6.9 for a schematic view of pathways in the binocular vision system.

So how will V1 neurons respond to the outline of the house? A V1 neuron that is tuned to 45-degree tilted lines and has its receptive field in the position along the roof may fire strongly to the angled roof. A V1 neuron that responds best to vertical will help signal the presence of the vertical wall and a horizontal neuron will respond to the ceiling or floor of the house. In this sense, it can be readily seen that V1 neurons do much more than respond to simple spots of light, as the LGN does. V1 neurons provide a *neural representation* of the orientation of visual features that comprise the contours and shapes of objects. Figure 6.10 provides a summary of the hierarchy of visual processing. From the LGN, V1,

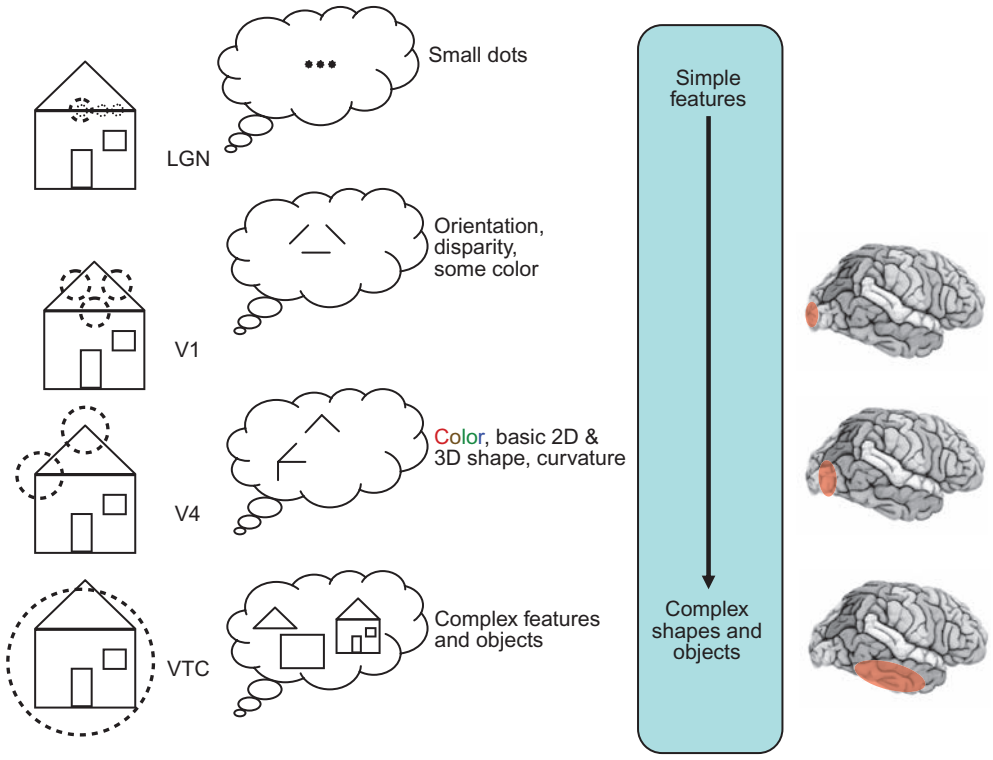


FIGURE 6.10 The hierarchy of visual processing. A demonstration of the hierarchical response properties of the visual system to simple and complex stimuli. The leftmost column shows our house stimulus and what receptive fields of each visual area we would see in the balloons. Not only do the receptive field sizes increase in each visual area, but also the complexity of the shapes they respond to. The rightmost column shows an estimate of where each area is in the brain. You can see that early visual areas respond to simple features and, as we move along the processing stream, areas respond to more complex shapes and objects. This is a well-established theme of the visual system. *Source*: Frank Tong, with permission.

V4 to the ventral temporal cortex, you can see that neurons gradually respond to more complex stimuli from one area to the next.

So, to summarize, V1 is important in analyzing the visual features at a fine level of detail. These neurons have small receptive fields that are sensitive to orientation, color, motion, or binocular disparity. After visual signals are analyzed in V1, they are sent to higher visual areas for further processing.

2.4 Extrastriate visual areas – outside of V1

V1 sends *feedforward* signals to many higher visual areas, including areas such as V2, V3, V4, and *motion-sensitive area MT*, to name a few (Figure 6.11) (Felleman and Van Essen, 1991). *Area V4* is known to be especially important for the *perception of color* (Zeki, 1977) and some neurons in this area respond well to more complex features or combinations of features (Pasupathy and Connor, 2002). For example, some V4 neurons are sensitive to curvature or to two lines that meet at a specific angle. These neurons might signal the presence of a curving contour or a corner. From our example of the house, a V4 neuron might respond best to the meeting of the two lines forming the point of the roof or to another corner of the house.

How then are these various bits and parts of the house, as represented by simple line orientations and corners, eventually represented as an entire object? Area V4 sends many outputs to higher visual areas in the *ventral visual pathway*, which is important for object recognition (Ungerleider and Mishkin, 1982). The anterior part of the ventral visual pathway consists of the ventral temporal cortex, which is especially important for object recognition.

2.5 Area MT

The middle-temporal area, or what is commonly called area MT (see Figure 6.11), is important for motion perception. Almost all of the neurons in area MT are direction-selective, meaning that they respond selectively to a certain range of motion directions and do not respond to directions beyond that range (Zeki, 1974; Albright, 1984). Moreover, some of these neurons respond well to

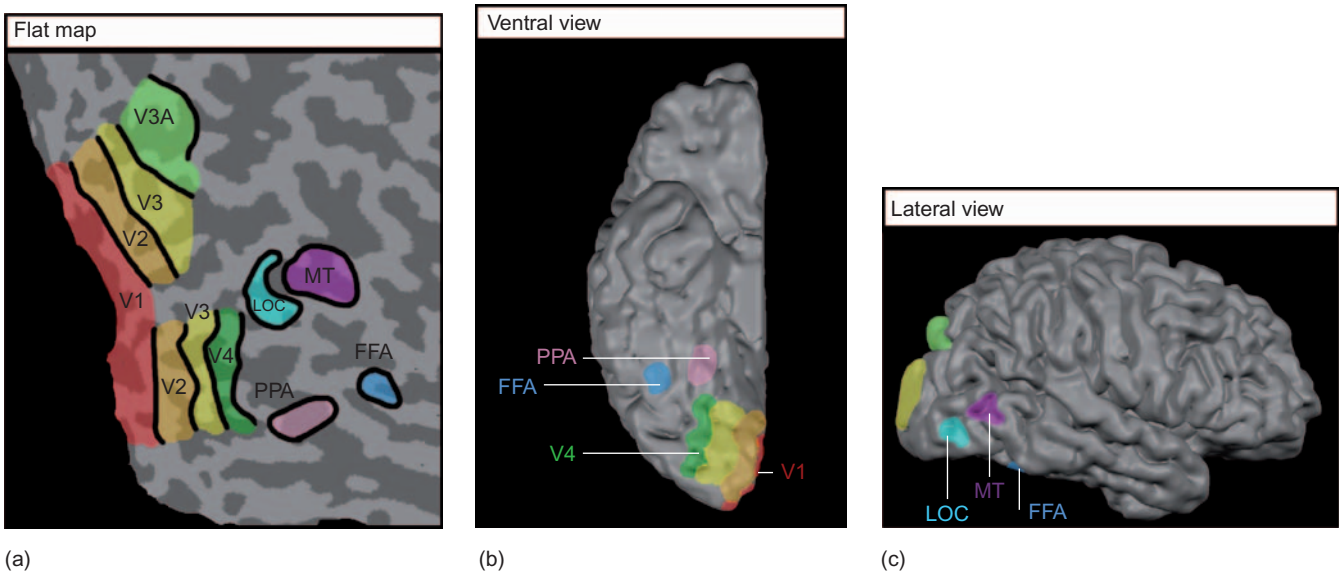


FIGURE 6.11 Visual areas of the brain. Functionally defined visual areas of the human brain, shown on a reconstruction from anatomical brain scans. (a) A flattened cortical representation of the human visual system. The flat map was created by unfolding the convoluted surface of the cerebral cortex, applying a cut through the calcarine sulcus, which divides area V1 into dorsal and ventral halves, and flattening the cortical sheet using computerized methods. This allows one to see all the visual areas of one hemisphere, including those buried in the sulci, in a single image. The upper half shows dorsal portions of visual areas V1, V2, and V3, as well as V3A. The lower half shows ventral visual areas V1, V2, V3, and V4, as well as the parahippocampal place area (PPA) and fusiform face area (FFA). Areas LOC and MT are also shown. (b) A ventral view of one hemisphere, showing the location of these areas in the cortex. (c) Lateral view of the same hemisphere, showing the positions of the different visual areas. (d) A medial view of the hemisphere showing mainly V1. *Source*: Squire *et al.*, 2003.

patterns of motion (Albright, 1992), meaning that these neurons can integrate many different motion directions and calculate what the overall direction of an object might be. As we will see, the activity in this region seems to be closely related to motion perception and, when activity in this region is disrupted, motion perception may be severely impaired.

2.6 The ventral and dorsal pathways: knowing what and where

The projections from V1 to higher areas in the cortex can be roughly divided according to two major parallel pathways: a *ventral pathway* leading from V1 to the *temporal lobe* that is important for representing '*what*' objects are and a *dorsal pathway* leading from V1 to the *parietal lobe* that is important for representing '*where*' objects are located (Figure 6.12).

This distinction between the ventral and dorsal pathways, sometimes referred to as the *what* and *where*

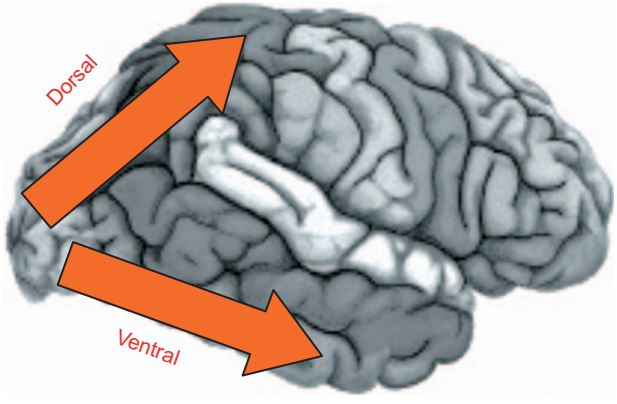
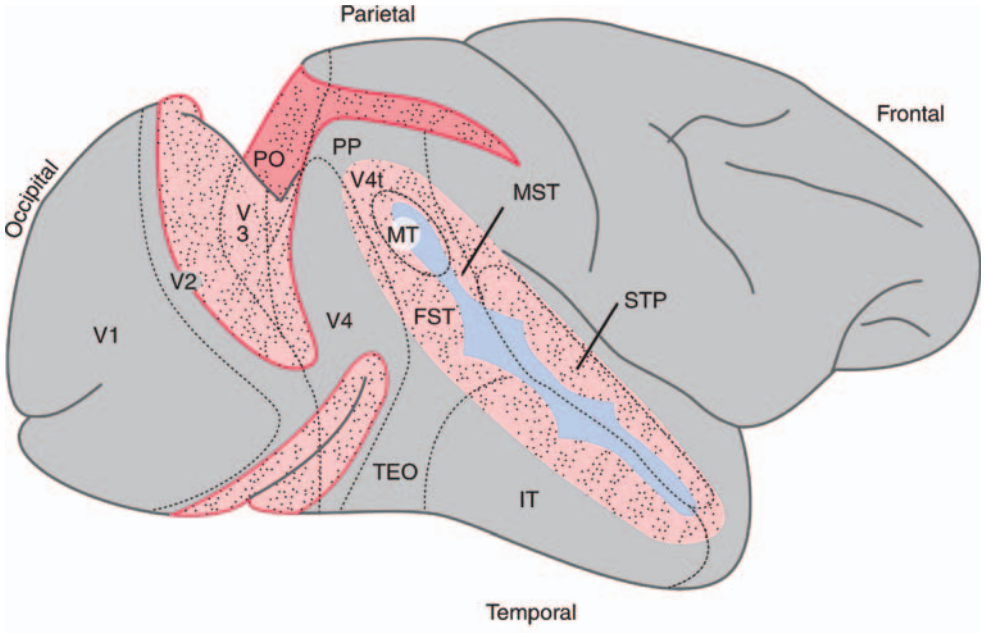
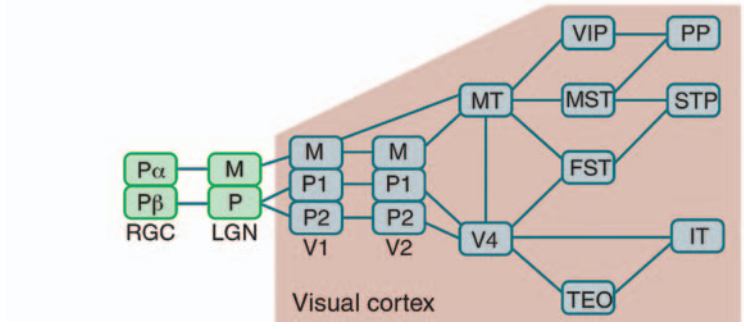


FIGURE 6.12 What and where pathways. The 'where' pathway is typically called the dorsal pathway because it includes dorsal areas like MT and the parietal cortex that are along the top of the brain. The 'what' pathway includes ventral areas like V4, LOC, and IT; hence it is known as the ventral processing pathway. These two pathways form a nice way of visualizing the flow of different cortical information. *Source*: Squire *et al.*, 2003.



(a)



(b)

FIGURE 6.13 Dorsal and ventral visual pathways. From the pioneering work of Ungerleider and Mishkin (1982), a schematic drawing of the dorsal and ventral pathways based on studies in monkey. (a) A lateral view of monkey brain, showing the location of primary vision cortex (V1), extra-striate cortex (V2–V4), and other key vision areas such as MT. (b) A schematic showing visual areas involved in dorsal and ventral processing streams. *Source*: Squire *et al.*, 2003.

pathways, respectively, is an important organizational principle of the visual system proposed by Ungerleider and Mishkin (1982) (Figure 6.13).

Support for this distinction comes from what has been discovered about the anatomical connections between visual areas in these two pathways, the response properties of visual areas in each pathway, and the visual deficits that can result from damage to the parietal or temporal lobe.

In the dorsal pathway, signals from V1 travel to dorsal extrastriate areas, such as area MT and V3A, which then send major projections to many regions of the parietal lobe. The dorsal pathway is important for representing the *locations* of objects, so that the visual system can guide actions toward those objects (Goodale and Humphrey, 1998). Consider what is involved in reaching for any object, such as a coffee mug sitting on a table; this type of vision requires detailed information about the precise location, size, and orientation of the object. Without such detailed information, you might reach toward the wrong location, your grasp might not match the size of the handle of the mug, or your hand might not be angled properly for gripping the handle. Areas MT and V3A are important for processing visual motion and stereo-depth, while specific regions in the parietal lobe are specialized for guiding eye movements or hand movements to specific locations in visual space.

In the ventral pathway, many signals from V1 travel to ventral extrastriate areas V2, V3, and V4 and onward to many areas of the temporal lobe. The ventral or 'what' pathway is important for processing information about the color, shape, and identity of visual objects, processing which emphasizes the stable, *invariant* properties of objects. For example, the ventral pathway is less concerned about the exact size, orientation, and position of the coffee mug; instead, its goal is to be able to identify such an object anywhere in the visual field and to be able to tell it apart from other similar objects (e.g. cups, bowls, teapots). We will be talking about the properties

of the ventral pathway in much greater detail, especially different regions of the temporal lobe.

While this dorsal-ventral pathway distinction is useful for grouping areas of the brain and understanding how much of the information flows back and forth between visual areas, it should not be taken as an absolute distinction. There is plenty of cross talk between the two pathways. Also, the parietal and temporal lobes send projections to some common regions in the *prefrontal cortex*, where information from each pathway can also be reunited.

2.7 Areas involved in object recognition

Single-unit recordings in monkeys have revealed that many neurons in the ventral temporal cortex respond best to contours, simple shapes, or complex objects. For example, some neurons in this region may respond best to square or round shapes, others to triangles and others still to even more complex figures, such as the outline of a house (see Figure 6.10), which looks like a triangle lying on top of a square. Some neurons in this region are highly selective and respond to only a particular kind of object, such as a hand, a face shown from a particular viewpoint, a particular animal, a familiar toy, or an object that the monkey has learned to recognize and so forth (Desimone *et al*., 1984; Gross, 1992; Logothetis *et al*., 1995; Tanaka, 1996).

Human neuroimaging studies have revealed many brain areas involved in processing objects. These object-sensitive areas, which lie just anterior to early visual areas V1–V4, respond more strongly to coherent shapes and objects, as compared to scrambled, meaningless stimuli. In this chapter, we will focus on three such brain areas (see Figure 6.10). The *lateral occipital complex* (LOC) lies on the lateral surface of the occipital lobe, just posterior to area MT. Because this region is strongly involved in object recognition, we will consider it as part of the ventral pathway, even though its position is quite dorsal when compared to other object areas. The *fusiform face area* lies on the fusiform gyrus, on the ventral surface of the posterior temporal lobe. The *parahippocampal place area* lies on the parahippocampal gyrus, which lies just medial to the fusiform gyrus on the ventral surface of the temporal lobe.

2.8 Lateral occipital complex (LOC)

The lateral occipital complex seems to have a general role in object recognition and responds strongly to a variety of shapes and objects (Malach *et al*., 1995). Figure 6.14 shows an example of the neural activity in LOC compared to V1. As the picture becomes more and more scrambled, V1 continues to respond and even gives a larger response, whereas activity in LOC declines. This shows that LOC prefers intact shapes and objects more than scrambled visual features.

This region seems to represent the particular shapes of objects. Presumably, different neurons in this region respond best to different kinds of objects. Because human brain imaging lacks the resolution to measure the object preferences of individual neurons, another method to test for object selectivity is to measure *neural adaptation* to a particular shape. This involves presenting two objects in a row – if the same object shape is presented twice in a row, then a region with object-selective neurons should adapt to the repeated shape and respond more weakly the second time around. This is exactly what LOC does, even when the repeated object is presented in a new location or in a different format so that retinotopic visual areas (V1–V4) won't adapt to the image (Grill-Spector *et al*., 1999; Kourtzi and Kanwisher, 2001).

2.9 Fusiform face area (FFA)

Neurophysiological studies have shown that face-selective neurons can be found in many parts of the temporal lobe of monkeys. Some of these *face cells* show remarkable precision in what they respond to and might respond best to a face of a particular identity, facial expression, or to a particular viewpoint of a face (e.g. right profile). Usually, these face cells can be found intermixed with neurons that respond to different types of objects, which led scientists to believe that there might not be a part of the brain that is dedicated to processing faces.

However, human neuroimaging studies have shown that there is a region in the fusiform gyrus, called the *fusiform face area* (FFA), that responds more strongly to faces than to just about any other category of objects (Kanwisher *et al*., 1997). This region responds more to human, animal, and cartoon faces than to a variety of non-face stimuli, including hands, bodies, eyes shown alone, back views of heads, flowers, buildings, and inanimate objects (Kanwisher *et al*., 1997; McCarthy *et al*., 1997; Tong *et al*., 2000; Schwarzlose *et al*., 2005). In a recent study, researchers tried scanning the brains of monkeys to see if they might also have a face-selective area in the ventral temporal cortex and it turns out that they do too (Tsao *et al*., 2006). The researchers could then record the activity of single neurons in this face area and discovered that 97 percent of the neurons in this region responded more to faces than to other kinds of objects. Moreover, these neurons were very good at telling apart different identities of faces but poor at telling apart different identities of objects, suggesting they may have an important role in recognizing and telling

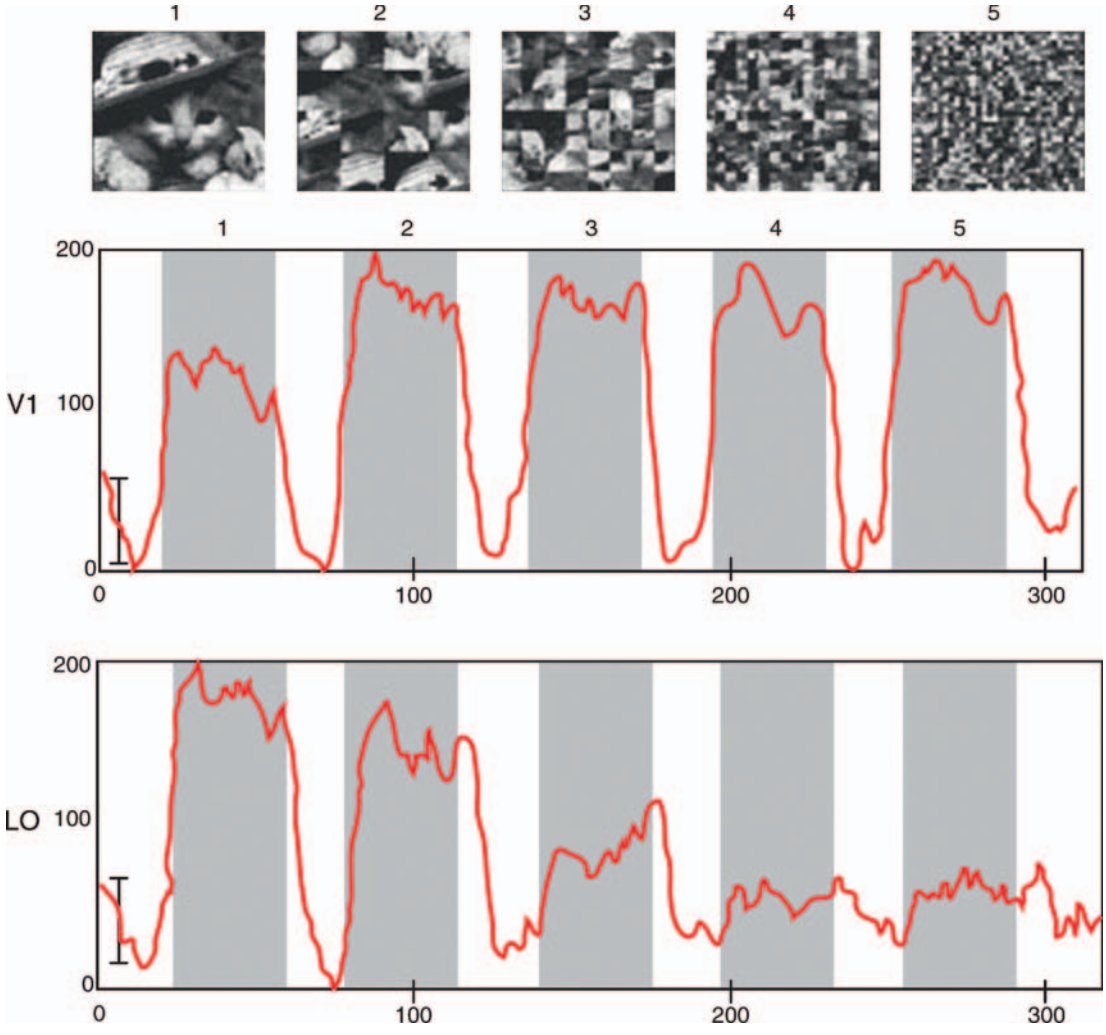


FIGURE 6.14 Neural response from low and high level areas. The response of primary visual cortex (V1) and lateral occipital (LOC) to a picture of a kitten at different coherencies. As the picture is scrambled V1 continues to respond – in fact, it actually increases its response once the image is scrambled. This demonstrates that it is not the image of the kitten which is driving responses in V1, but local patches of luminance and orientation. Conversely, the activity in lateral occipital cortex shows a large response to the kitten but, as the picture is scrambled, the activity in LOC drops down dramatically. This demonstrates that unlike V1, the activity in LOC is in response to the kitten. *Source*: Frank Tong, with permission.

apart different faces. Because this region is very small, this highly face-selective region that consists almost entirely of face cells was never discovered before. As we will see, this region seems to be important for the conscious perception of faces.

2.10 Parahippocampal place area (PPA)

The parahippocampal place area (PPA) is another strongly category-selective region that responds best to houses, landmarks, indoor and outdoor scenes (Epstein and Kanwisher, 1998). In comparison, this brain area responds more weakly to other types of stimuli, such as faces, bodies or inanimate objects. Because this region responds to very different stimuli than the fusiform face area, many studies have taken advantage of the different response properties of the FFA and PPA to study the neural correlates of visual awareness, as we will see later.

3.0 THEORIES OF VISUAL CONSCIOUSNESS: WHERE DOES IT HAPPEN?

So is it possible to say where along this cascade of neural activity consciousness is really happening? Is it possible to point to a particular set of neurons or a

BOX 6.1 Humans perceiving humans: neural correlates of biological motion

Have you ever spotted a friend in a crowd simply because you recognized something in the way he or she moved, walked, or gestured? Is there something special in the way human beings perceive motion that is specific to our species, as opposed to other motion – like a wave breaking at the shoreline, a flag waving on a flagpole, or an airplane moving through the sky?

Vision researchers have long asked these and related questions about human visual perception. An early problem to address was: How do you investigate visual perception that is *specific* to human biological motion and not related to any other aspect of visual perception of the human form? A Swedish scientist developed an innovative way to do just that: In 1973, Gunnar Johansson published an article entitled 'Visual perception of biological motion and a model for its analysis' that has sparked decades of studies on the topic of biological motion perception. Dr. Johansson developed a method to attach small points of light to strategic places on his research assistant – shoulders, elbows, hands, knees, and feet – who was wearing dark-colored clothing. He filmed his assistant while moving about the dimly lit laboratory, creating stimulus sets that contained only the moving points of light (see Figure 6.15).

Results of these early point-light motion studies and many more since have shown that, yes, we humans are quite skilled at perceiving each others' motions. The intriguing aspect of these studies is that no single light can give information about how the person is moving: it requires all the lights (or many of them at least). Follow-up studies have provided evidence that not just biological motion is perceived using point-light stimulus sets: observers can report the gender (Kozlowski & Cutting, 1977; Mather & Murdock, 1994; Troje, 2002), emotional state (Dittrich, Troscianko, Lea, & Morgan, 1996), and even the size (Jokisch & Troje, 2003) of the "point-light person."

Is biological motion perceived in the same brain areas where other types of motion are processed? Although there are many brain areas that are active for visual motion, evidence has emerged from several laboratories that *biological motion* activates a region in the posterior superior temporal sulcus (STSp) as one area that seems specifically sensitive to biological motion (Bonda, Petrides, Ostry, & Evans, 1996; Howard, Brammer, Wright *et al*., 1996; Vaina *et al*., 2001).

In particular, the research of Professor Emily Grossman at the University of California, Irvine, has shed light on the brain areas and neural networks that underlie biological motion (Grossman, Battelli, & Pascual-Leone, 2005; Grossman & Blake, 2001, 2002a, 2002b; Grossman, Blake, & Kim, 2004; Grossman, Donnelly, Price *et al*., 2000).

But, is STSp specialized for processing *human* biological motion? Grossman and her colleagues are looking into this matter more closely, and recently reported that STSp was more responsive to point-light human motion as compared to point-light motion produced by multijointed but nonhuman "creatures" (Figure 6.16) (Pyles, Garcia, Hoffman, & Grossman, 2007). Thus, they concluded that the STSp is indeed a region specialized for encoding *human biological motion* and not just *complex motion* or *animation*.

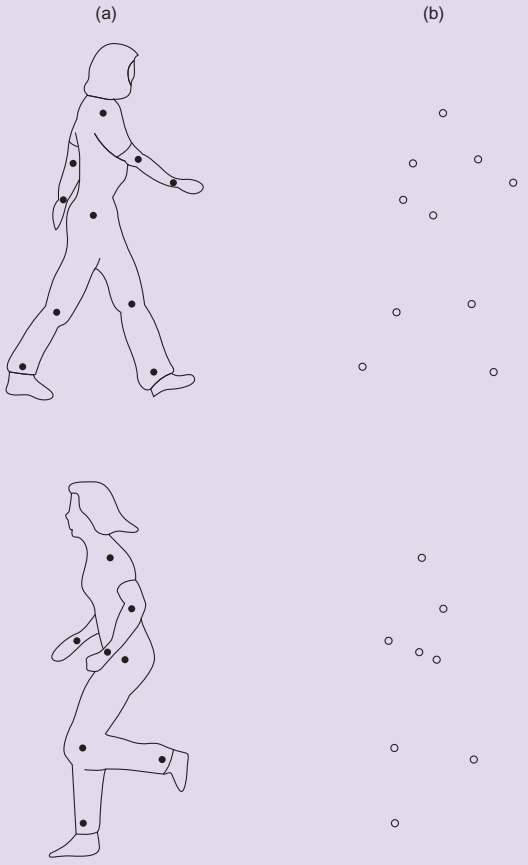


FIGURE 6.15 The original figure from Johannson, (1973), showing the location of the points of light on a human (a) and how they looked when the human form was removed (b). *Source*: Johannson, 1973.

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BOX 6.1 (Continued)

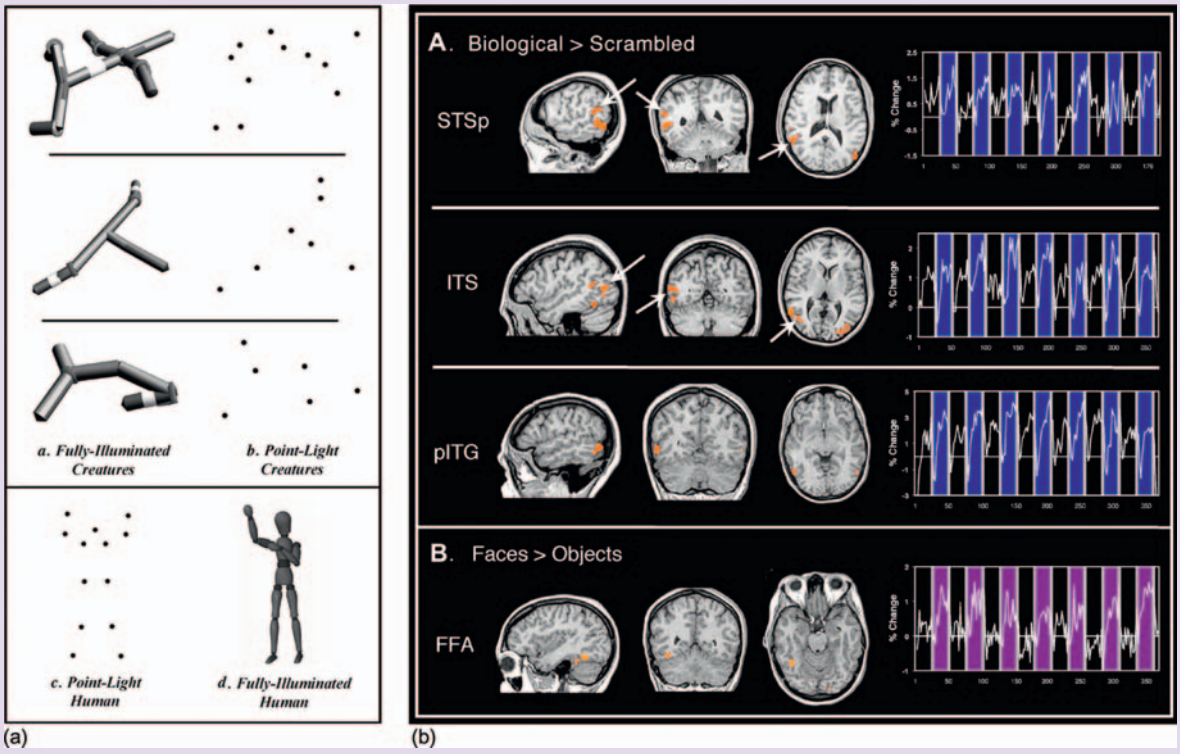

FIGURE 6.16 Left panel: The stimuli used in Pyles *et al*. (2007) showing three fully illuminated "creatures" and their point-light animation, and the human and corresponding point-light animation. Right panel: Brain results for the "creatures" and human biological motion study. Note on the top panel that area STSp is more active for the human biological motion than the scrambled motion. *Source*: Pyles *et al*., 2007.

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Howard, R. J., Brammer, M., Wright, I., Woodruff, P. W., Bullmore, E. T., & Zeki, S. (1996). A direct demonstration of functional specialization within motion-related visual and auditory cortex of the human brain. *Current Biology*, *6*, 1015–1019.

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particular brain area and say, *There it is . . . , there is the place in my brain where I am experiencing the visual world in my mind*?

It turns out that the answer is not so simple, but scientists are gathering important clues. Even if a person's eyes are closed or a person can no longer see because of damage to the eyes or to the LGN, it is still possible for a person to 'experience seeing' if electrical stimulation is applied to their primary visual cortex. In other words, it is possible to bypass stimulation of the retina and the LGN and induce visual experiences by directly stimulating area V1.

Is it possible to bypass the primary visual cortex and induce a clear visual experience? We don't know the definite answer yet but, so far, the answer seems to be 'no'. Primary visual cortex seems to be important for our ability to consciously perceive any visual feature, while higher visual areas may have a more specialized role in perceiving certain visual features or objects (Tong, 2003). As we will see in the remainder

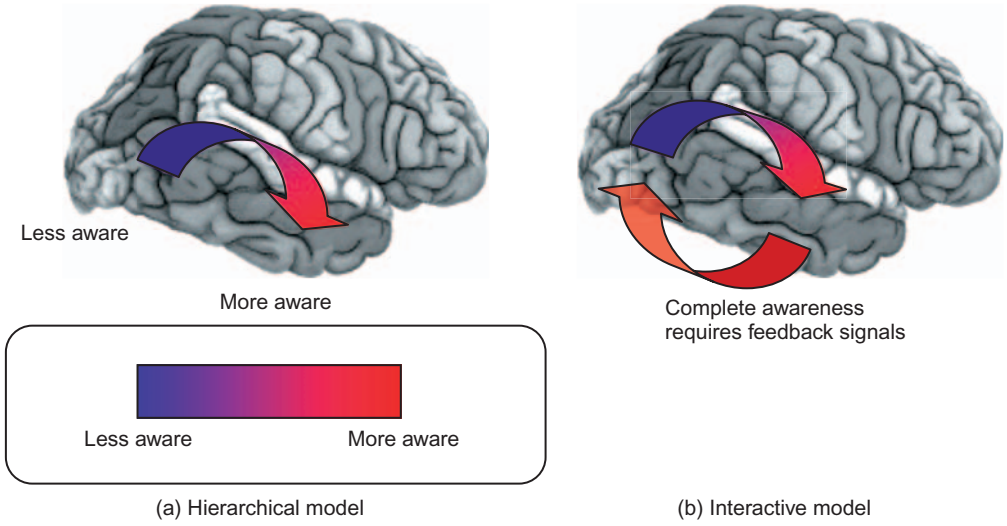


FIGURE 6.17 Hierarchical and interactive models of visual awareness. (a) In the hierarchical model, with each step further in visual processing, awareness is more likely to result from that processing. (b) In the interactive model, feedback signals from later processing areas to earlier processing areas are needed to attain awareness. At present, it is not clear which of the two models best describes the way brain activity results in visual awareness. *Source*: Frank Tong, with permission.

of this chapter, different cortical visual areas seem to play different roles in our conscious visual experience. An emerging view is that many of the same brain areas and neurons involved in processing specific kinds of visual stimuli, such as orientation, motion, faces, or objects, are also involved in representing these types of stimuli in consciousness. Many neurons are more active when a person is conscious of seeing a stimulus than when the stimulus is shown but fails to reach consciousness. So far, there doesn't seem to be any single area in the brain that is solely responsible for consciousness. Instead, many brain areas seem to work together to achieve this remarkable feat. Brain areas involved in attentional processing are also important for the ability to perceive and respond to visual and other sensory inputs, a topic that will be covered in Chapter 8.

3.1 Hierarchical and interactive theories of vision

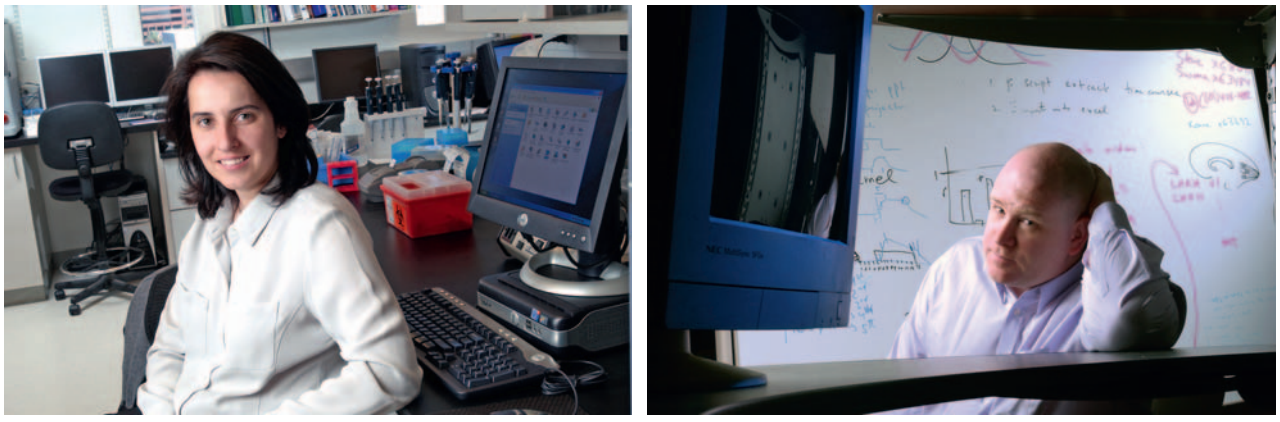
According to one theory of visual consciousness, called the *hierarchical theory* (Crick and Koch, 1995; Rees *et al*., 2002), consciousness is organized in a hierarchical fashion with increasingly higher visual areas being more closely related to our internal conscious experience (Figure 6.17a). This theory is consistent with the notion that higher visual areas respond to more complex stimuli, such as entire objects, and can integrate information about many visual features, which are processed in early visual areas. However, if this is the case, how is it that we can be aware of specific visual features or very fine spatial details, information that is best represented in early visual areas such as V1?

The *interactive theory* of visual consciousness emphasizes a different idea. It turns out that the signals entering the brain do not simply travel up the visual hierarchy: higher visual areas send feedback signals back down to early visual areas, especially to area V1 (Bullier, 2001). There are as many *feedback projections* in the visual system, neurons projecting from higher visual areas to lower visual areas, as there are *feedforward projections*. According to the interactive theory, once a stimulus is presented, feedforward signals travel up the visual hierarchy, activating many neurons in its path, but this feedforward activity is not enough for consciousness. Instead, high-level areas must send feedback signals back to lower-level areas where the feedforward signals came from, so that neural activity returns full circle, forming a neural circuit (Figure 6.17b) (Pollen, 1999; Lamme and Roelfsema, 2000). Why might this combination of feedforward-feedback signals be important for awareness? This may be because higher areas need to check the signals in early areas and confirm if they are getting the right message, or perhaps to link neural representations of an object to the specific features that make up the object.

So far, it is not clear which theory will prove true and odds are that both theories capture some parts of the bigger picture. An emerging view is that our conscious experience may reflect the distributed pattern of brain activity involving many visual areas, a kind of dialogue between neurons in early visual areas, including V1, and high-level areas such as those in the ventral temporal cortex and the parietal lobe. That said, the contribution of each brain area may be somewhat different or in some cases, unique. The next parts of this chapter will describe the highlights of this story.

FRONTIERS OF COGNITIVE NEUROSCIENCE

Eye movements and visual fading



(a) (b)

FIGURE 6.18 (a) Susana Martinez-Conde, Laboratory of Visual Neuroscience, Barrow Neurological Institute, Phoenix, AZ, USA. (b) Stephen L. Macknik, Laboratory of Behavioral Neurophysiology, Barrow Neurological Institute, Phoenix, AZ, USA.

Visual fading is a phenomenon in which an unchanging visual stimulus disappears from perception. The neural substrate of visual fading is neural adaptation, by which visual neurons decrease or cease their responses to unchanging visual stimuli.

Visual fading and neural adaptation

Nervous systems have evolved to detect changes in the environment. We can detect stationary objects only because the images projected onto our retinas are never stationary for long: even during visual fixation, our eyes are never still.

To experience visual fading, we must remove the effects of eye movements, so that the visual images of unchanging objects remain stable on the retina, leading to the adaptation of neuronal responses.

Visual fading under retinal stabilization conditions

To achieve *perfect* retinal stabilization, we must eliminate *all* eye movements. This is complicated because our eyes are in constant motion (Figure 6.19(a)). Even when we fixate our gaze precisely on an object of interest, we nevertheless constantly produce small involuntary eye movements, called fixational eye movements (Figure 6.19(b)). These tiny eye movements are usually sufficient to prevent neural adaptation and visual fading.

Holding a subject's eyes physically stationary (with paralyzing drugs, for instance) is technically very difficult, and potentially hazardous to the subject's health. Therefore, retinal stabilization studies generally have used an alternative approach: to shift the visual stimulus in such a way that all eye movements are effectively nulled. That is, the visual stimulus must move in the same direction, speed, and amplitude as the eye, so that the retinal image remains stable despite eye movements.

Early stabilization experiments reported that images faded only after several seconds of stabilization. However, Coppola and Purves (1996) more recently showed that the images of retinal vascular shadows (which are extremely stable with respect to the eye) disappear in less than 80 msec, suggesting that normal visual processing entails a very rapid mechanism for image creation and erasure.

Visual fading without retinal stabilization

Although perfect retinal stabilization is most easily achieved under laboratory conditions, fading of stationary objects, especially in the visual periphery, occurs quite often in everyday vision. In 1804, Swiss philosopher Ignaz Paul Vital Troxler noted that deliberately focusing the gaze on something causes stationary images in the surrounding region gradually to fade away (Figure 6.19(c)).

Martinez-Conde *et al*. (2006) showed that Troxler fading occurs due to the suppression of microsaccades (the largest and fastest type of fixational eye movement) during precise and sustained fixation. Microsaccade production dropped just before a visual target vanished, indicating that a lack of microsaccades leads to neural adaptation and fading. Conversely, microsaccade production peaked right before the target reappeared. These results demonstrated for the first time that microsaccades have a

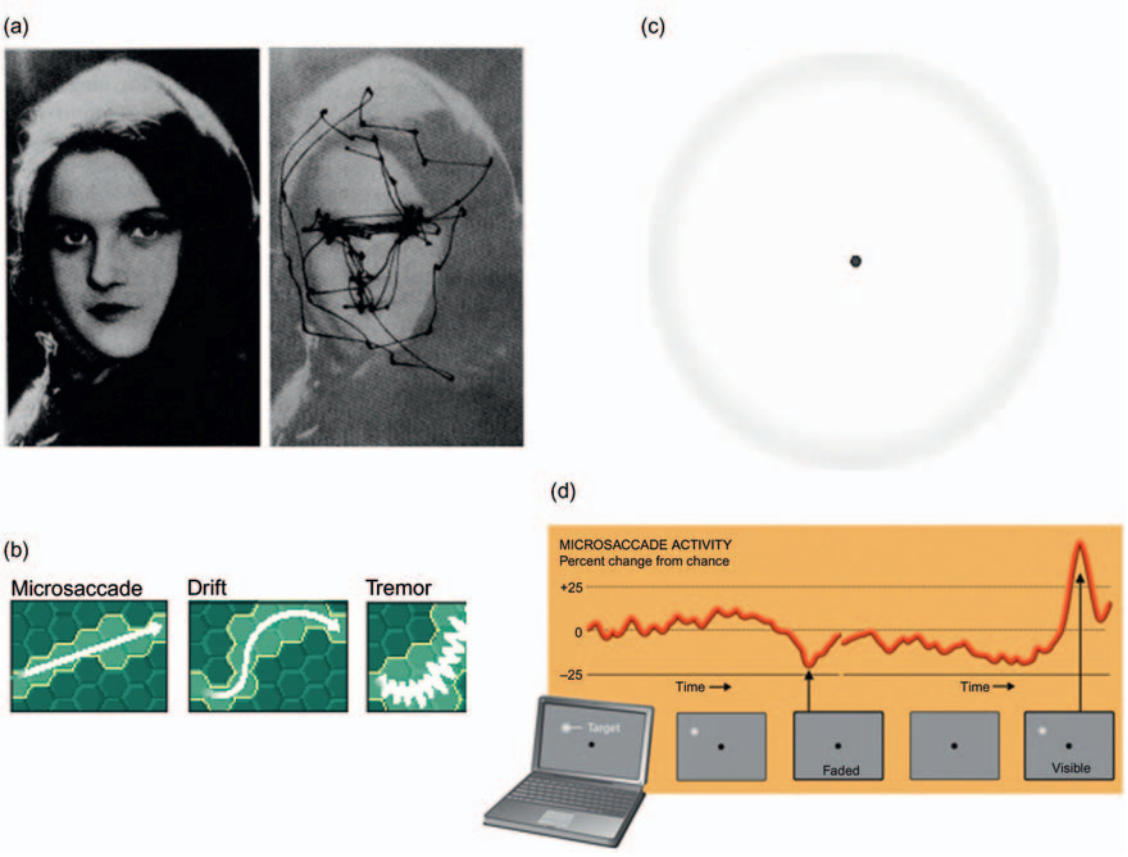


FIGURE 6.19 Eye movements and visual fading. (a) An observer views a picture (left) while eye positions are monitored (right). The eyes jump, seem to fixate or rest momentarily, producing a small dot on the trace, then jump to a new region of interest. The large jumps in eye position illustrated here are called *saccades*. However, even during fixation, or "rest" times, eyes are never still, but continuously produce fixational eye movements: drifts, tremor, and microsaccades. *Source:* Yarbus, 1967. (b) Cartoon representation of fixational eye movements in humans and primates. Microsaccades (straight and fast movements), drifts (curvy slow movements), and tremor (oscillations superimposed on drifts) transport the visual image across the retinal photoreceptor mosaic. *Source:* Martinez-Conde & Macknik, 2007. (c) Troxler fading. In 1804, Swiss philosopher Ignaz Paul Vital Troxler discovered that deliberately fixating on something causes surrounding stationary images to fade away. To elicit this experience, stare at the central dot while paying attention to the surrounding pale ring. The ring soon vanishes, and the central dot appears set against a white background. Move your eyes, and it pops back into view. *Source:* Modified from Martinez-Conde, Macknik, & Hubel, 2004. (d) Microsaccades bring about visibility when people are fixing their gaze. Subjects stared at a small spot in the center of a computer screen, causing a static peripheral target to vanish from their view and then reappear. Just before the target vanished, the viewers' microsaccades became sparser, and right before it reappeared, these eye movements became more frequent. *Source*: Martinez-Conde and Macknik, 2006.

critical role in driving visibility during visual fixation (Figure 6.19(d)).

Implications for visual consciousness

Fixational eye movements counteract the visual fading of stationary objects and drive their visibility during fixation. Thus, fixational eye movements can help constrain the spatiotemporal characteristics of stimuli that are consciously visible. Moreover, the neural responses triggered by fixational eye movements along the visual pathway must encompass the neural code for visibility.

Suggested further readings

1. Coppola, D., & Purves, D. (1996). The extraordinarily rapid disappearance of entopic images. *Proceedings of the National Academy of Sciences of the United States of America*, *93*, 8001–8004.
2. Martinez-Conde, S., & Macknik, S. L. (2007). Windows on the mind. *Scientific American*, *297*, 56–63.
3. Martinez-Conde, S., Macknik, S. L., & Hubel, D. H. (2004). The role of fixational eye movements in visual perception. *Nature Reviews Neuroscience*, *5*, 229–240.
4. Martinez-Conde, S., Macknik, S. L., Troncoso, X., & Dyar, T. A. (2006). Microsaccades counteract visual fading during fixation. *Neuron*, *49*, 297–305.
5. Yarbus, A. L. (1967). *Eye Movements and Vision* (B. Haigh, Trans.). New York: Plenum Press.

4.0 BRAIN AREAS NECESSARY FOR VISUAL AWARENESS: LESION STUDIES

In the previous section, we learned about how the neurons in different visual areas respond best to certain visual features, objects, or spatial information. Such findings from single-neuron recordings or human neuroimaging may indicate that a particular brain area has a role in processing a certain type of stimulus, but cannot reveal whether that brain area is actually *necessary* for perceiving that stimulus. Perhaps that brain area could be removed without causing any troubles with perception. For example, if multiple brain areas are involved in processing a particular visual feature (e.g. motion), then damage to any single brain area might not impair the ability to perceive that feature because other intact brain areas would be able to compensate for the loss.

Brain lesion studies are important for understanding what brain areas may be necessary for certain kinds of visual awareness – awareness of color, motion, faces, objects, or the capacity to be aware of seeing anything at all! Brain lesions may be performed experimentally, in animal studies, or may be investigated in humans who have suffered from unfortunate injury to certain parts of the brain, which may result from strokes, tumors, trauma, or neurodegenerative diseases. Visual deficits resulting from damage to certain parts of the visual system can be very debilitating. However, by studying these patients, it may be possible to understand the neural causes of their impairment, which may inform scientists about brain function and eventually lead to new ways to help treat such impairments.

4.1 Consequences of damage to early visual areas

Different visual deficits can result from neural damage at different levels of the visual processing hierarchy. Damage to the retina or optic nerve of one eye can result in monocular blindness – the loss of sight from one eye. Damage to the LGN, the optic radiations that travel to V1, or V1 itself, can lead to loss of vision in the contralateral visual field (see Figure 6.7). Damage to a small part of V1 can lead to a clearly defined scotoma, a region of the visual field where perception is lost. The first retinotopic maps of V1 were actually constructed by mapping the trajectory of bullet wounds of soldiers injured in the Russo-Japanese war and World War I; there was a clear relationship between the location of each case of scotoma and the part of V1 that was injured (Inouye, 1909; Holmes, 1918).

4.1.1 V1 and blindsight

Do lesions to V1 lead to a complete loss of visual function? In 1965, researchers investigated this question in a rhesus monkey named Helen, after the majority of visual cortex was removed. For the initial 19 months, Helen displayed behavior that suggested she was completely blind. Gradually however, it seemed that her vision was returning. In time, she could navigate among objects in a crowded room and even reach out to catch a passing fly. Initially, she would only look at and reach for objects when they moved. Then, as time passed, she responded to flashing lights, then a stationary light source, and, finally, a stationary dark object against a light background (Humphrey and Weiskrantz, 1967; Humphrey, 1974). This is an excellent example of how *recovery of function* can occur after brain injury. Helen was able to locate salient objects, but seemed unable to recognize them.

Was Helen aware of what she saw, or was she able to perform visually guided actions despite a lack of visual awareness? It is difficult to ask an animal if it is conscious of something or not, but a recent study of monkeys with unilateral V1 lesions suggests that they might not be aware of what they see. In this study, monkeys were able to report the locations of objects in their 'blind' hemifield accurately if they were forced to make a choice between two options. However, if they were given the choice of reporting whether an object was presented or not and an object was sometimes presented in the good hemifield, in the blind hemifield, or not at all, they would fail to report objects presented in the blind hemifield (Cowey and Stoerig, 1995; Stoerig *et al*., 2002). It is as if these objects were not 'seen'.

Interestingly, humans with V1 lesions may show similar above-chance performance, even though they report a lack of visual experience in their blind hemifield. Patient DB suffered extreme migraines because of a venous tumor lodged in his right calcarine cortex (V1). Surgical removal of the tumor led to the loss of his right primary visual cortex. As you might expect, this procedure left him practically blind in his left visual field. Interestingly, however, when he was systematically tested in his blind hemifield, his performance suggested otherwise.

Weiskrantz *et al*. (1974) reported that when DB was asked to point to a target in his blind visual field, DB claimed he could see nothing at all, yet he could point quite accurately to the location of the light source. He could also accurately report whether a stick was angled vertically or horizontally. This ability to perform visual tasks at above-chance levels, despite the patient's reports of lacking any visual impressions, is known as *blindsight*. In different experiments, his task was to discriminate between Xs and Os. His performance was quite accurate and improved as a function of the size and duration of the stimuli. During all these experiments DB insisted that he saw nothing. Interestingly, when pressed, he reported sometimes having the feeling of 'smoothness' or 'jaggedness' in discriminating the Xs and Os, but denied that these feelings were associated with any visual experience. So how is this possible? How can DB point to or discriminate visual stimuli without being able to see them?

These findings suggest that there can be dissociations between visual processing in the brain and a person's subjective awareness – sufficient information is reaching DB's visual system to allow him to make forced-choice discriminations, but this information is not sufficient to support awareness (Weiskrantz, 1986). However, one concern is whether visual awareness is completely absent in blindsight. Patients might be reluctant to report weak visual impressions that are nonetheless sufficient for making forced-choice discriminations. Similar effects can occur in normal subjects under near-threshold conditions. Some blindsight patients report residual impressions of salient moving stimuli, which they describe as 'black moving on black', but normally they report seeing nothing when shown static stimuli. Vision in blindsight is severely degraded, but not always completely absent.

Intact extrastriate cortex may be crucial for blindsight, as patients who have had an entire hemisphere removed show little evidence of residual visual abilities (Faubert *et al*., 1999). Although the pathway from retina to LGN to V1 provides the vast majority of visual input to cortex, several alternative *subcortical* pathways project to extrastriate areas, bypassing V1. Single-unit recordings in monkeys indicate that visual information can still reach extrastriate areas after V1 has been lesioned. Although firing rates are reduced, a substantial proportion of neurons in motion area MT and V3 remain selectively responsive to visual stimuli (Rodman *et al*., 1989; Girard *et al*., 1991). Recent neuroimaging studies show that unperceived stimuli presented to the blind hemifield still evoke robust fMRI responses from motion-sensitive area MT, color-sensitive area V4 and regions involved in object perception (Goebel *et al*., 2001). Thus, considerable stimulus selectivity is maintained in extrastriate cortex, yet this activity appears insufficient to support awareness in the absence of V1. This is consistent with the predictions of *interactive models*. However, it remains possible that extrastriate signals are too weak or degraded to support conscious perception but sufficient to support forced-choice discrimination.

4.2 Extrastriate lesions – damage outside area V1

Lesions to V1 can eliminate almost all visual awareness in the corresponding areas of visual space, even though sufficient visual information seems to be reaching extrastriate areas to support blindsight behavior. This in itself informs us as to the role of V1 in the mediation of visual awareness. So what happens when extrastriate areas are damaged? See Figure 6.20 for a schematic map of visual areas and corresponding deficits.

4.2.1 Motion blindness

Perhaps because we are so sensitive to seeing motion, it is very rare for brain damage to lead to a complete loss of motion perception. However, there is a striking example of one patient who can no longer perceive motion after suffering strokes leading to large bilateral lesions that encompassed area MT and extensive surrounding areas. For this patient, the world appeared to be a series of still snapshots, like living in a strobe-lit world. Simple tasks like crossing the street became dangerous, because she could not tell how fast the cars were approaching (Figure 6.21(a)). Even pouring a cup of coffee became a challenge, since she couldn't tell how fast the liquid was rising, so the cup would overflow.

Other studies have found that smaller lesions just to area MT usually lead to more moderate deficits in the ability to perceive motion and both patients and animals may also show considerable recovery over time (Plant *et al*., 1993; Pasternak and Merigan, 1994). So it seems that area MT is very important for motion perception, but other visual areas can contribute to motion perception even when MT is damaged.

4.2.2 Cortical color blindness

Damage to ventral area V4 can lead to cortical color blindness or what is sometimes called *achromatopsia*

(Meadows, 1974a; Bouvier and Engel, 2006). Patients report that the world appears to be drained of color, almost like shades of gray, perhaps like the illustration in Figure 6.21(b). These patients can still perceive the boundaries between colors, but have difficulty with identifying the colors themselves. Achromatopsia is typically associated with lesions that include area V4 and possibly regions just anterior to area V4. Damage to one hemisphere can even lead to selective loss of color perception in the contralateral visual field.

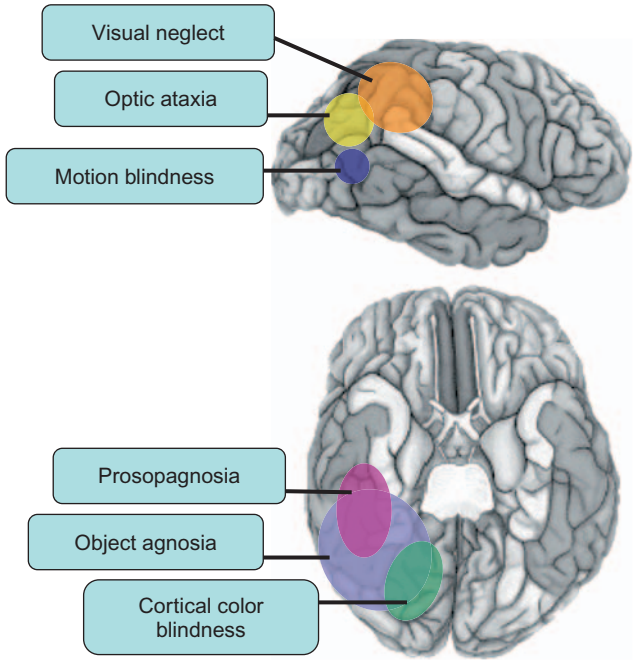


FIGURE 6.20 Visual deficits and brain areas. The areas of the brain in which damage can result in the associated visual deficit. Here, the areas are only shown on one hemisphere, although for some deficits like motion blindness, damage to both hemispheres is required. *Source*: Frank Tong, with permission.

4.3 Damage to ventral object areas

4.3.1 Visual agnosia

Patients with *visual agnosia* have difficulties with recognizing objects because of impairments in basic perceptual processing or higher-level recognition processes. Such patients can still recognize objects by using other senses such as touch, hearing, or smell, so the loss of function is strictly visual. The word *agnosia* can be translated from Greek as meaning 'to lack knowledge of', so visual agnosia implies a loss of visual knowledge.

Here, we will discuss three types of visual agnosia: apperceptive agnosia, associative agnosia, and prosopagnosia. Patients with *apperceptive agnosia* can still detect the appearance of visually presented items, but they have difficulty perceiving their shape and cannot recognize or name them. These patients usually fail at shape-copying tests and may have difficulty copying very simple shapes, such as a circle, square, or perhaps even a single tilted line. Carbon monoxide poisoning is a frequent cause of apperceptive agnosia, as this can lead to profuse damage throughout the occipital lobe.

Remarkably, some apperceptive agnosics show evidence of unconscious visual processing of visual features they cannot consciously perceive. Goodale *et al*. (1991) tested an apperceptive agnosic patient, DF, who had difficulty reporting the orientation of simple lines or real objects. When asked to report the orientation of a narrow slot cut into the face of a drum, she was unable to report the angle of the slot and made many errors (Figure 6.22, top panel; the drum was rotated

(a) (b)

FIGURE 6.21 Color and motion blindness. (a) Damage to motion area MT in both hemispheres can lead to a loss of motion perception: *akinotopsia*. Patients describe seeing multiple still frames instead of smooth motion. This can make simple tasks like crossing the road challenging and dangerous. (b) Damage to color areas in only one hemisphere of the cortex can result in a loss of color perception to one side of visual space. Cortical color blindness is called *achromatopsia*. *Source*: Frank Tong, with permission.

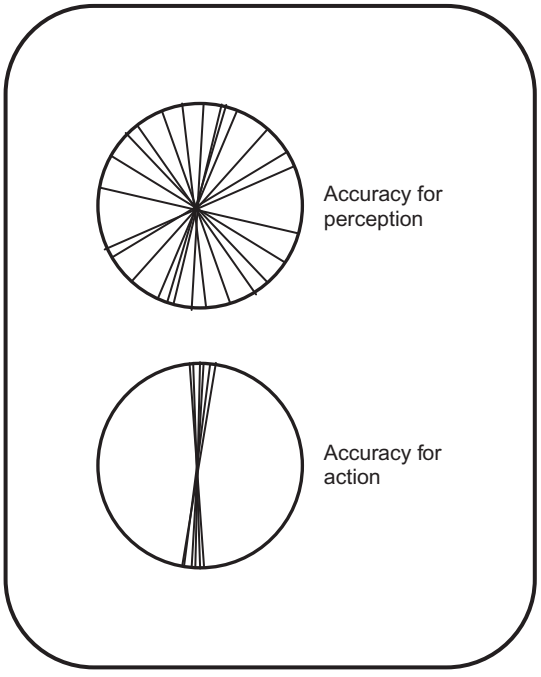


FIGURE 6.22 She can do it, but can't report it. Results from subject DF. Each line represents one of DF's attempts at either matching the orientation of a mail slot or actually posting a letter into it. The top panel shows DF's attempts at matching the orientation of the slot to the card (no execution of action). Here, the lines are distributed around the circle suggesting that DF had trouble in perceiving the orientations. However, the lower panel shows DF's accuracy in posting the card into the oriented slot, adjusted so that each correct orientation is vertical. Because the lines are all grouped around vertical, this suggests that DF is accurate when executing the action of posting. Patient DF can post the letters with no problem; her hand knows what to do. But when asked to match the orientation of the slot, DF performs very badly. *Source*: Frank Tong, with permission.

to a new orientation on each trial). However, when asked to post a card through the slot, she could do so with remarkable accuracy (Figure 6.22, lower panel) and was even surprised by her own ability to do so. Surprisingly, when she was asked just to hold the letter by her side and rotate it to match the angle of the slot, her performance was poor once again and she reported that the slot seemed 'less clear' than when she was allowed to post the card. What can account for this behavioral dissociation between DF's ability to report the angle of the slot and to perform a visually guided action?

Patient DF provides strong evidence to suggest that there are separate pathways for processing 'what' an object is and 'where' it is with respect to performing a visually guided action. According to Goodale and Milner, patient DF has damage to the ventral visual pathway but intact processing in the dorsal pathway, a claim that has recently been supported by brain imaging studies (James *et al.*, 2003). They propose that the dorsal system is not only responsible for processing 'where' objects are, but also 'how' actions can be performed toward a particular object, such as pointing or reaching for that object. Apparently, visual processing in the dorsal system is not accessible to consciousness – the patient can't report the orientation of the slot – yet the dorsal system can guide the right action. Complementary studies of patients with *optic ataxia* have revealed the opposite pattern of visual deficits, indicating a *double dissociation* between conscious visual perception and visually guided action. Optic ataxia typically results from damage to the parietal lobe, which is part of the dorsal pathway. These patients can perceive visual orientations and recognize objects well, but have great difficulty performing visually guided actions.

Associative agnosia refers to the inability to recognize objects, despite apparently intact perception of the object. For example, when asked to copy a simple picture, patients with associative agnosia manage to do a reasonable job, especially if given enough time. In comparison, this task would almost be impossible for an apperceptive agnosic.

Dr. Oliver Sacks described a patient who, as a result of brain injury, 'mistook his wife for a hat'. The patient had great difficulty identifying objects, even though his vision was otherwise normal and he could describe the features of what he saw. When presented with a rose from Dr. Sacks' lapel, the patient described it as 'a convoluted red form with a linear green attachment', but only upon smelling it did he realize that it was a rose. When his wife came to meet him at the doctor's office, he accidentally reached for her head when he wanted to retrieve his hat from the coat rack (Sacks, 1985).

Associative agnosia usually results from damage to the ventral temporal cortex. Typically, associative agnosics will have difficulty recognizing a variety of objects, especially objects that are all from a single category, such as faces. However, as we will see below, this is often but not always the case.

Although most patients with visual agnosia will have difficulty with recognizing both faces and objects, there are some remarkable exceptions that have been reported. Patients with *prosopagnosia* are still able to recognize objects well, but have great difficulty recognizing or telling apart faces (Bodamer, 1947; Meadows, 1974b). Deficits can be severe; some prosopagnosic patients can no longer recognize close family members or friends and, instead, must rely on other cues such as the person's voice or clothing to recognize that person.

Some patients can no longer recognize their own face in photos or even in the mirror.

Is prosopagnosia really due to a specific impairment in face recognition? Maybe face recognition is just more difficult than other forms of object recognition. After all, faces are very visually similar to one another – every face has the same basic shape and configuration of features, whereas objects are much more distinct from one another (see Box 6.2 for discussion).

Studies have revealed a few patients who can discriminate between subtle differences in objects but can no longer distinguish between faces. For example, a prosopagnosic farmer became very poor at recognizing human faces but could still recognize the different sheep in his flock (McNeil and Warrington, 1993). Another patient could no longer recognize upright faces accurately and was actually better at recognizing upside-down faces, which is just the opposite of normal subject performance (Farah *et al*., 1995). What might be the reason for this? According to one theory, the brain may have specialized mechanisms for processing upright faces, whereas upside-down faces are processed by a general object recognition system (see the face inversion demonstration in Figure 6.23). So, if the face recognition system is damaged in a prosopagnosic patient, then this system might lead to automatic errors when the patient is presented with an upright face. However, upside-down faces would not be automatically processed by this system, thereby allowing the object recognition system to take over the task.

Perhaps the strongest evidence for some separation between face and object recognition systems comes from a study of a very unusual object agnosic patient, CK, who was very impaired at recognizing objects but could recognize upright faces just as well as normal subjects (Moscovitch *et al*., 1997). Remarkably, if the faces were turned upside-down, CK became severely impaired, performing six times worse than normal participants under these conditions. Apparently, CK has an intact system for processing upright faces, but the system responsible for processing objects and upside-down faces is badly damaged. Taken together, evidence from patient CK and prosopagnosic patients provides evidence of a double dissociation between the visual processing of upright faces as compared to objects and upside-down faces.

What type of brain damage leads to prosopagnosia? Prosopagnosia can result from bilateral damage around the regions of the lateral occipital cortex, inferior temporal cortex, and the fusiform gyrus (Meadows, 1974b; Bouvier and Engel, 2006). In some cases, unilateral damage to the right hemisphere may lead to this impairment. Because lesions are usually quite large and might damage fiber tracts leading to a critical brain region, it is difficult to identify a precise site. Nonetheless, the brain lesion sites associated with

BOX 6.2 How are faces and objects represented in the brain?

There are two primary theories about how the visual system manages to process and recognize objects and faces. The brain could either do it in a *modular* fashion, with distinct modules for processing faces, or the processing could be done in a *distributed* way across multiple areas of the ventral temporal cortex. According to the modular view, object perception is broken down into neural modules, specific areas of the brain that specialize in processing a particular object category. Research suggests that the fusiform face area (FFA) might be a specialized module for the processing and recognition of upright faces (Kanwisher *et al*., 1997; Tsao *et al*., 2006). In addition, an area that responds to the presentation of places (e.g. a house) seems also to be a specialized module (Epstein and Kanwisher, 1998). This area has become known as the parahippocampal place area (PPA). This trend for modular representation of objects does not span every object; in fact, it is primarily observed only in the two above-mentioned cases. For example, there is not a banana or shoe area in the human brain.

An interesting twist on the modular hypothesis is the *expertise hypothesis*, which proposes that the so-called fusiform face area is actually specialized for expert object recognition (Gauthier *et al*., 2000). We probably spend more time looking at faces than at any other object (especially if you include watching faces on TV). Just stop a moment and think about how much information you can get from all the subtle changes in someone's face when you're talking to him or her and you soon realize you are indeed a face expert. It has been proposed that the FFA is responsible for the recognition process of any object we are 'experts' at. Research shows that, while looking at pictures of birds, bird experts show somewhat stronger activity in the FFA than do non-bird experts (Gauthier *et al*., 2000). Whether the FFA is specific for face recognition or any object of expertise, both cases involved a specialized structure that is distinct from regions of the ventral temporal cortex involved in object processing. Look at the two faces in Figure 6.23 – do you notice anything strange? Now turn the book upside down and look again – now do you see it? This is an example of the face inversion effect. When faces are upside down we are really bad at identifying them. This is an example of how specialized we are at face perception.

The other hypothesis is that the brain processes faces and objects in a distributed way across multiple areas in the ventral pathway. A study by Haxby and colleagues

BOX 1.1 (Continued)

FIGURE 6.23 The face inversion effect. Demonstration of how bad we are at recognizing upside down faces. Look at the two pictures of Barack Obama. Do you notice anything strange? Now turn the page upside down and look again. Now you should see that one of the pictures has been severely distorted. This effect, called the face inversion effect, demonstrates just how specialized our visual system is for processing upright faces.

demonstrated that regions outside of the FFA still show differential responses to faces, as compared to other types of stimuli (Haxby *et al*., 2001). Even if the response difference between faces and different objects is quite small in many of these areas, there is enough information across all of these regions outside of the FFA to tell the difference between faces and objects. However, neuropsychological evidence of double dissociations between face recognition and object recognition are difficult to explain according to this account. One possible resolution is that the activity of highly face-selective neurons in regions such as the FFA may be important for telling apart subtle differences between individual faces, but that more distributed activity patterns outside of these highly face-selective regions are enough for telling apart basic differences between faces and objects and perhaps more obvious differences between faces (e.g. male versus female, young versus old).

prosopagnosia appear to encompass the fusiform face area and extend much more posteriorly.

4.4 Damage to dorsal parietal areas

Damage to the posterior parietal lobe (or superior temporal gyrus) can lead to a striking global modulation of visual awareness called *neglect*, in which a patient completely ignores or does not respond to objects in the contralateral hemifield (Driver and Mattingley, 1998). Patients with right parietal damage may ignore the left half of the visual field, eat just half of the food on their plate, or apply make-up to just half of their face. They may also ignore sounds or touches coming from their left.

This syndrome can resemble a disorder of visual perception. However, neglect happens in the absence of damage to the visual system and can involve multimodal deficits, including motor and tactile deficits.

Moreover, when patients are instructed to attend to the neglected field they can sometimes respond to these stimuli (Posner, 1980). So this syndrome is more a deficit of *attention* than an inability to perceive stimuli. Without specific cuing, patients find it difficult to perceive objects in their neglected field. We will not spend much time delving into the many interesting facets of visual attention as an entire chapter is dedicated to it (see Chapter 8).

Bilateral lesions to parietal areas can lead to a much more profound deficit called *Balint's syndrome*, which is primarily a disruption of spatial attention. It can be characterized by three main deficits: (1) *optic ataxia*, the inability to point to a target; (2) *ocular apraxia*, the inability voluntarily to shift gaze; and (3) *simultanagnosia*, the inability to perceive more than one object in the visual field simultaneously, even when the objects occupy a common region of space. People with Balint's syndrome can often appear blind because, in fact, they can only focus on one region of visual space or one object at a time and find it hard voluntarily to shift their attention to different locations. These results again highlight the importance of attention-related brain areas in supporting visual awareness.

5.0 LINKING BRAIN ACTIVITY AND VISUAL EXPERIENCE

At any given moment, millions of neurons are firing in the visual part of your brain. The activity of some of these neurons is probably closely linked to what you are consciously perceiving here and now, while the activity of other neurons may be far removed from immediate experience. If scientists could somehow isolate the neurons that closely reflect a person's conscious experience, would this reveal which neurons or brain areas are central to consciousness and which are not? This search is for the neurons that *correlate* with changes in perceptual awareness or consciousness; hence it has been called the search for the *neural correlates of consciousness* or the NCC for short (Crick and Koch, 1995).

The first challenge involves telling apart *stimulus-driven activity* from activity linked to awareness. Not all visual responses are conscious, as can be told from the fact that many visual areas respond well to stimuli even when an animal is anesthetized.

How then is it possible to measure awareness-related activity and separate this from any possible unconscious activity that is driven by the visual stimulus itself? There are many tools scientists can use for this purpose. The next section will discuss some of the most popular and useful methods for isolating neurons whose activity correlates with changes in visual awareness.

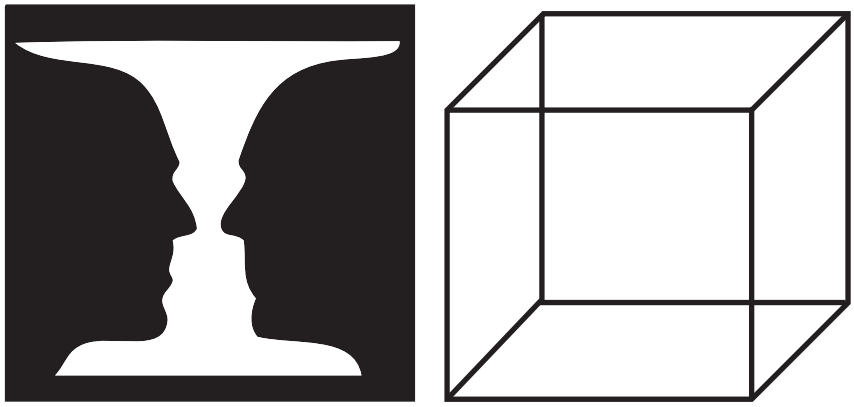
5.1 Multistable perception

Have you ever been in the dark, perhaps lying in bed, staring at some strange shape across the room? At one moment it might look like a person, then like some strange static animal, then like a rock statue. After racking your brain to identify this mysterious object, you finally hit the light switch and lo and behold it's only the dim light catching your jacket on the chair. In this example, when vision was difficult and *ambiguous*, perception did something uncommon – it faltered or alternated between different things. This is an example of *multistable perception*: the jacket on the chair (the physical stimulus) did not change while your perception of it did! This kind of situation is a valuable tool, as it enables scientists to study changes in visual awareness independent of any changes in the visual stimulus.

There are many examples of *multistable patterns* or ambiguous figures that scientists can use to investigate these neural correlates of consciousness. Patterns that primarily have only two primary interpretations are called *bistable patterns* (Figure 6.24). Try to see if you can perceive both interpretations of each ambiguous figure, the face and the vase and the two views of the Necker cube. Bistable perception can still occur if you keep your eyes fixed on a single point in the middle of the stimulus. In this case, the image on your retinas – and hence the stimulus-driven activity – is pretty much constant over time, while your perception fluctuates. By looking for brain areas that show activity changes correlated with perceptual changes, scientists can identify the neural correlates of consciousness.

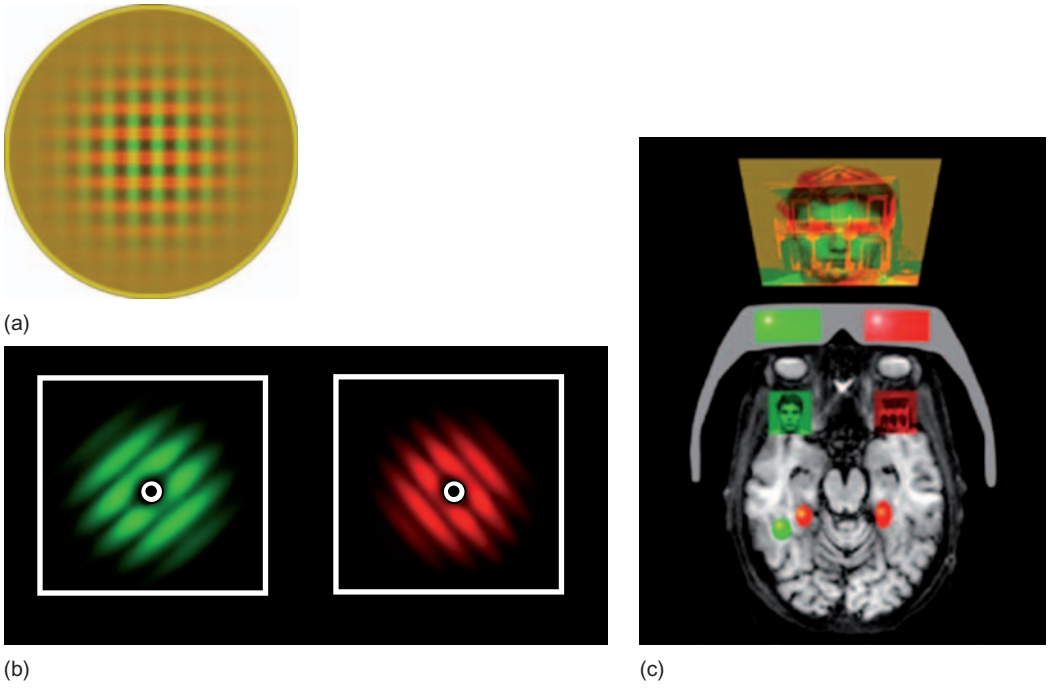
5.2 Binocular rivalry: what you see is what you get activated

One of the most powerful and best-studied examples of bistable perception is a phenomenon called *binocular rivalry*. When two very different patterns are shown, one to each eye, because they are so different the brain cannot fuse them together like it would normally do. What then happens is quite striking: awareness of one pattern lasts for a few seconds, then the other pattern seems magically to appear and wipe away the previously visible pattern. It is like the two patterns are fighting it out in the brain for your perceptual awareness! If you can get your hands on a pair of red-green filter glasses then



(a) (b)

FIGURE 6.24 Bistable figures. (a) After looking at this figure for a while you will notice that there are two interpretations. One is a central vase; the second one silhouettes of two faces looking in at each other. This image is bistable: while you look at it your perception will alternate between the vase and the faces. (b) This wireframe cube, typically known as the Necker cube, has two equally likely spatial interpretations. Perception tends to alternate between the configuration of the closest side projecting upward and the closest side projecting downward. Like the vase and silhouettes above, this is bistable. This bistability allows a dissociation of low level stimulation and awareness. The physical pattern does not change, but your awareness of it does!



(a) (b) (c)

FIGURE 6.25 Binocular rivalry. (a) If you have a pair of red-green filter glasses, this image should produce binocular rivalry. Your awareness should alternate back and forth between vertical and horizontal striped patterns. (b) If you don't have a pair of red-green glasses, try cross-fusing these two patterns. To cross-fuse, you need to cross your eyes so the two patterns line up and appear to be on top of one another. The surrounding squares can help you do this. Line up the square outline and the bull's-eye dot in the middle. (c) Schematic of how Tong *et al*. (1998) used red-green glasses to attain binocular rivalry in the fMRI scanner and the FFA and PPA where they found activity that correlated with awareness. *Source*: Frank Tong, with permission.

you can experience binocular rivalry by viewing Figure 6.25(a). Otherwise try cross-fusing the two patterns in Figure 6.25(b). (To cross-fuse, try letting your eyes cross so the two patterns appear one on top of the other. The dots in the center and surrounding square should fuse. If these demos work for you, you should see one pattern, while the other is completely invisible, almost like closing one eye and then the other.)

What happens in the brain during binocular rivalry? Tong *et al*. (1998) tackled this problem by focusing on

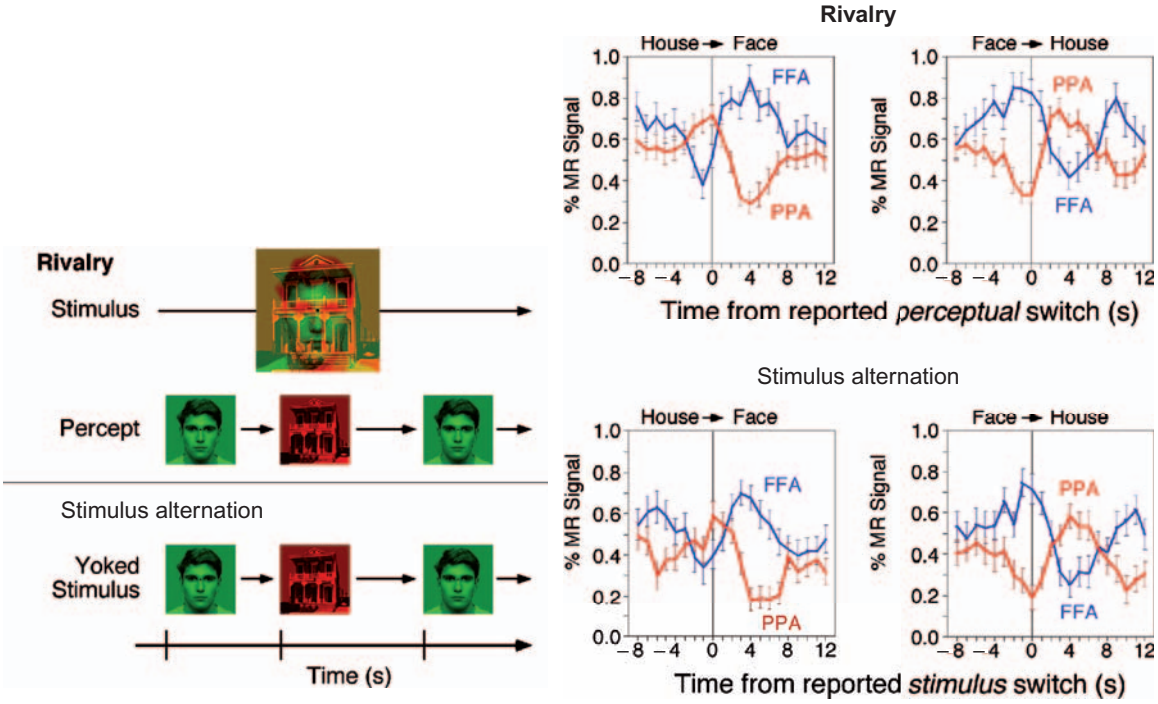


FIGURE 6.26 The stimuli and data from Tong *et al*. (1998). (a) Top panel shows the binocular rivalry condition. Subjects experienced first the face, then the house, then the face, etc. Lower panel shows a control condition with no binocular rivalry; the images were switched on and off the screen. (b) Top panel shows the fluctuations in activity in both the FFA (blue) and PPA (red) during binocular rivalry. When each image became perceptually dominant, activity in the corresponding area increased. Lower panel shows the neural response in the same areas to the control condition with no binocular rivalry. The alternations in activity in both conditions were around the same size. *Source*: Tong *et al*., 1998.

two category-selective areas in the ventral temporal lobes, the FFA and the PPA. They used red-green filter glasses to present a face to one eye and house to the other eye while measuring fMRI activity from these brain areas (Figure 6.25(c)). In this study, participants might first perceive the house, then flip to the face and then back again – as is typical of binocular rivalry (Figure 6.26(a)). Remarkably, the FFA was active only when subjects reported that they saw the face. Likewise, the PPA was active only when the participants reported that they saw the picture of the house (Figure 6.26(b)). Next, the researchers tested physical alternations between two the pictures, switching one picture on while switching the other off. The resulting stimulus-driven responses in the FFA and PPA were about the same strength as those measured during binocular rivalry and, surprisingly, no stronger. It seems that the activity in these brain areas closely mirrors what the observer perceives during rivalry and doesn't reflect the temporarily suppressed stimulus that is still activating the retina.

Other brain imaging studies have found that activity at earlier stages of visual processing is closely linked to what the observer perceives during binocular rivalry. For example, strong awareness-related modulations have been found in human V1 (Polonsky *et al*., 2000; Tong and Engel, 2001), and even in the lateral geniculate nucleus (Haynes *et al*., 2005; Wunderlich *et al*., 2005). These results favor the notion that activity in early visual areas may be important for awareness, as is suggested by the *interactive model*. However, scientists are still trying to discover whether the interactive model or hierarchical model of awareness is a better description of the way the brain works.

Another approach is to train monkeys to report which of two patterns is dominant during binocular rivalry (Figure 6.27). This takes some training but can be done by providing fruit juice rewards for the monkey. Then, while the monkeys report their perception during rivalry, researchers can measure the activity of single neurons in different parts of the brain. These studies find strong modulations in the ventral temporal cortex that match the monkey's reported perception during rivalry (Sheinberg and Logothetis, 1997). In fact, around 85 per cent of the neurons recorded in the temporal lobe showed these modulations.

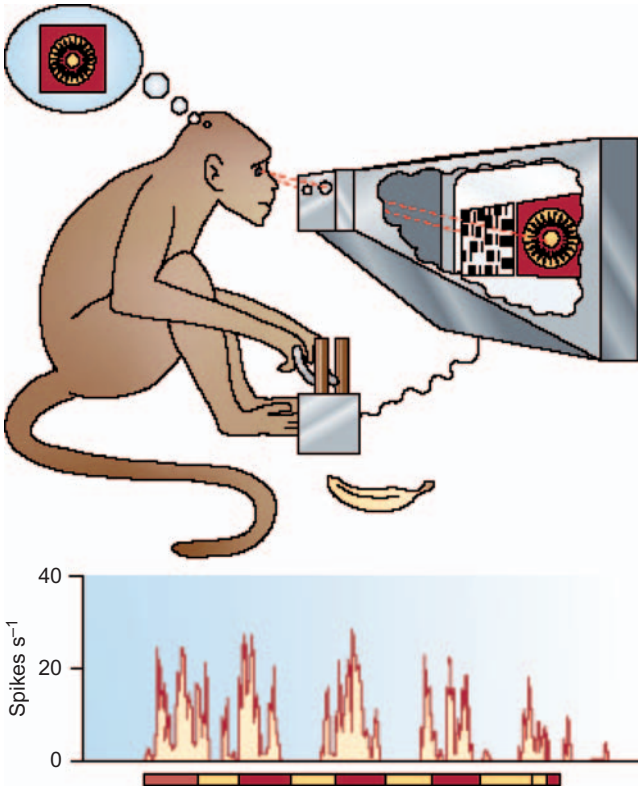


FIGURE 6.27 Monkeys and binocular rivalry. Illustration of monkey doing a perceptual binocular rivalry task, while researchers record from neurons in the monkey's brain, as in Sheinberg and Logothetis, 1997. *Source:* Blake and Logothetis, 2002.

Although related studies have found weaker effects of rivalry in the early visual areas of monkeys (Leopold and Logothetis, 1996), the studies described above reveal that it is indeed possible to study the neural correlates of consciousness in both monkeys and humans.

5.3 Visual detection: did you see it?

Another way to separate physical stimulation and perceptual awareness is to get people to do a *visual detection* task. Here, a subject has to detect and say when he or she sees a particular pattern. The researcher makes the pattern harder and harder to see, so on different instances the pattern might be easy to see while at others times almost impossible and sometimes it won't even be there. Because this task gets difficult, people will get it wrong sometimes. There will be occasions when someone reports seeing the pattern when it wasn't even presented and other times when he or she will miss the pattern and report seeing nothing. When this kind of experiment is done in the fMRI scanner, we can see the pattern of brain activity corresponding to the visual pattern. Also, when no pattern is displayed and subjects report that they don't see the pattern (*true negative*), we don't see that type of brain activity for the pattern. However, what do you think happens when someone gets it wrong? This is the case when no pattern is actually presented but the subject thinks he or she saw something and so reports 'yes the pattern was there' (*false positive*). Interestingly, activity in areas V1, V2, and V3 closely follows what we think we saw. In other words, on trials where a faint stimulus is presented but the subject fails to detect it, activity is much weaker in these areas (Ress and Heeger, 2003). However, if no stimulus is presented but the subject mistakenly thinks that a faint stimulus was presented, it turns out that activity is greater in V1, V2, and V3 on these trials.

What accounts for these fluctuations in activity level from trial to trial? This has been attributed to trial-to-trial variability in neural activity or *neural noise* in the system. Your memory of the pattern could 'shape' the random neural activity present in sensory areas, tipping the balance and making you think you saw the pattern. This is another example of how the brain's activity may closely reflect the phenomenal experience of seeing something, even when nothing was actually presented. This is interesting because it demonstrates that it doesn't matter what physical pattern is presented to a person; what does matter is what is happening in the brain!

5.4 Constructive perception: more to vision than meets the eye . . .

If you drive a car then you probably know what a blind spot is – for the driver it's the area behind the car that cannot be seen in the side or rear view mirrors. Our eyes also have a *blind spot*, at the back of the retina where the axons of the retinal ganglion cells meet to form the optic nerve as it exits the eye (see Figure 6.3(b)). There are no photoreceptors in the blind spot and hence we are blind in that area.

It is easy to demonstrate the blind spot. Look at the diagram in Figure 6.28(a). Close your left eye, look directly at the cross with your right eye, and move the textbook close to your nose. Then move it slowly away from your face, while keeping your eye fixed on the cross. At the right distance, which should be around 12 inches (30 cm) away from the page, you should notice the dot vanish. As the image of the dot on your retina moves into the blind spot, it disappears!

(a) (b)

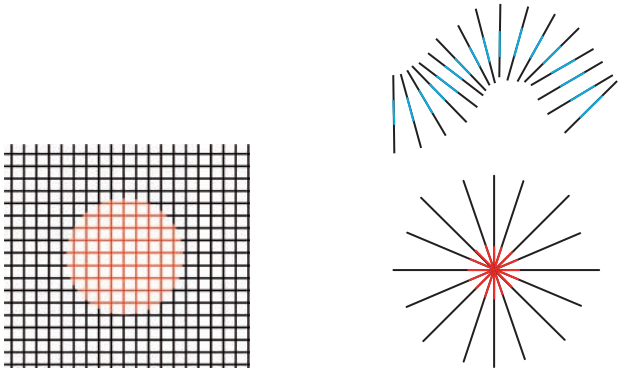
FIGURE 6.28 Demonstrations of the blind spot. (a) Close your left eye, look directly at the cross with your right eye, move the page up close to your nose, and then move it slowly away from your face, while keeping your eye fixed on the cross. At the right distance, which should be around 12 inches (30 cm) away from the page, you should notice the red dot vanish. As the image of the dot on your retina moves into the blind spot, which has no photoreceptors, it disappears! (b) Likewise, notice how the black stripes now fill in; they become joined and the red dot vanishes. *Source*: Frank Tong, with permission.

Hopefully this demonstration worked on you, and perhaps you are thinking . . . . wait a minute, if there is a blind spot in my vision all the time then why don't I see a hole in my vision when I look around at things with one eye covered? Well, the brain does something remarkable, it actually *fills in* perception of the blind spot. The brain uses the visual information from around the blind spot to infer what should be in the blind spot and it constructs awareness of what it 'thinks' should be there. Filling in at the blind spot is an example of *constructive perception* or *perceptual filling in*.

Another way to demonstrate the filling in can be seen by viewing Figure 6.28(b). Move the page around until the gap between the lines is in the blind spot. When each group of lines is abutting the blind spot, what you will see are continuous long lines. The red dot should be replaced by one continuous set of lines. The brain fills in the path of the lines so you don't see the red dot in the gap anymore. This is a case of perceptual filling in; the brain actively creates the perception of a complete object from the separate segments that lie on either side of the blind spot.

Perceptual filling in not only happens in the blind spot, but also occurs in other parts of the visual field. Notice how the area between the colored lines in Figure 6.29(a) somehow appears colored. However, careful inspection reveals that this background area is actually just white – no color at all. This illusion is called *neon color spreading* and the experience of color here seems to come from constructive filling-in mechanisms at work in the visual cortex. Recent brain imaging studies have found that activity in V1 is greater in corresponding regions where subjects perceive neon color spreading (Sasaki and Watanabe, 2004). This suggests that neurons as early as V1 may be important for perceptual filling in and our experience of color, even illusory colors.

During another type of filling in known as *visual phantoms* (Figure 6.29(b)), our visual system can also fill in gaps between two patterns. In Figure 6.29(b), you may have the impression of dark bands continuing



(a)

(b)

FIGURE 6.29 Demonstrations of perceptual filling in. (a) In these three examples the background is white – it has no color. However, you might notice that the red and the blue tend to fill in, coloring the white background. (b) The light patches and dark patches in the top and bottom panels tend to give the impression of light and dark sectors along the center strip, even though the center strip is a uniform gray. This illusion works much better when moving. *Source*: Frank Tong, with permission.

across the blank gap, even though there is no stimulus being presented there at all. Using moving stimuli can further enhance the visual phantom illusion. When we experience this type of filling in, cortical areas V1 and V2 respond as if a real pattern were being presented in the gap (Meng *et al.*, 2005).

The brain can fill in not only color and patterns but also motion. If you flash a spot of light in one location,

then follow it by a similar flash at a different location at the appropriate time, observers experience the illusion of movement – *apparent motion*. This kind of trick is used all the time in overhead shop signs and it's the basis for why movies look so smooth and real. If you look at the actual film running through the projector you will find that there is a series of stills that are flashed onto the screen one after another: the experience of smooth motion is simply an illusion. Recent studies have found that the perceived path of apparent motion is represented by neural activity in V1 (Jancke *et al*., 2004; Muckli *et al*., 2005). As with the previous examples of color and pattern, the brain seems to fill in apparent motion both perceptually and neurally, even when there is no physical motion occurring.

From the above examples, it should be clear that the brain can actively construct perceptual representations, even when there is no physical stimulus presented in a particular region of the visual field. Filling in appears to occur in early visual areas, as early as V1, suggestive that early visual areas may provide the basis for constructive visual experiences.

5.5 Neural correlates of object recognition

What brain areas are important for object recognition? As we saw in the study of binocular rivalry, activity in the fusiform face area and parahippocampal place area is closely linked to the observer's awareness of faces and houses. Similarly, if subjects are presented with ambiguous figures such as those shown in Figure 6.24(a), regions of the ventral temporal cortex show greater activity when recognition switches to the other interpretation. For example, when viewing Rubin's face-vase display, switches to the face percept lead to increases in activity in the fusiform face area.

Other studies have investigated awareness of visually masked objects, which are so briefly presented that they can just barely be recognized. When observers are able successfully to recognize a briefly flashed object, activity is greater in many regions of the ventral temporal cortex than when recognition is unsuccessful (Grill-Spector *et al*., 2000; Bar *et al*., 2001). Also, if observers are shown an ambiguous black and white image, like a Mooney face shown in Figure 6.30, right panel, which when shown at different orientations is hard to recognize, activity is much greater in ventral temporal areas when subjects become aware of the hidden object (Dolan *et al*., 1997; McKeeff and Tong, 2006). Interestingly, in most of these studies, early visual areas don't show a difference between conditions in which observers perceive the object or not. Perhaps

FIGURE 6.30 These images are called Mooney faces. They are originally made from photos of real faces. Because these face images can be hard to recognize, they are useful in studying object recognition. When people do finally recognize the face, you see an increase in neural activity in the fusiform face area. *Source*: Frank Tong, with permission.

what is even more remarkable, when subjects are simply asked to imagine a face, this can lead to activation of the fusiform face area (O'Craven and Kanwisher, 2000). Likewise, imagining a place or landmark can activate the parahippocampal place area. These studies suggest that simply retrieving a visual memory of a particular object can activate these object areas.

6.0 MANIPULATIONS OF VISUAL AWARENESS

In the previous section, we discussed *correlational methods* of studying conscious perception that relied on finding the neural correlates of consciousness. Knowing that activity in area A correlates with perception B (e.g. seeing leftward motion) provides *correlational evidence* that area A is involved in representing perception B. However, something can be correlated with a particular function without being causal. For example, the engine of a car roars whenever it is working hard, but the roaring sound of the engine isn't what makes the wheels turn. Dampening the sound of the engine won't stop the car from moving, but disrupting the pistons from moving will.

To provide further evidence of the role of a brain area in consciousness, we need to provide *causal evidence* showing that manipulating the activity in area A can *produce* or *disrupt* perception B. There are many causal methods in neuroscience, which involve inducing or disrupting activity in a certain brain area, either temporarily or permanently (e.g. lesion studies). This next section will highlight some of the findings from manipulations of neural activity and visual awareness.

Electrical stimulation of the occipital lobe can elicit subjective visual sensations or what are called *phosphenes*. For example, blind patients who had electrical implants in primary visual cortex reported having their first visual experience in years when this area was stimulated. When small regions were stimulated, the subjects reported seeing phosphenes that looked like 'small grains of rice held at arm's length'.

This seems obvious if we remember that the language of the brain is really electrical. Neurons communicate via weak electrical currents, hence when a current is applied to a collection of neurons it is not surprising that the person experiences some sensation. There are many ways to do this: during a surgical operation neurons can be electrically stimulated or, on a larger scale, an electrical current can be passed through the skull. However, a more recent and less invasive method is transcranial magnetic stimulation (TMS).

6.1 Transcranial magnetic stimulation

Transcranial magnetic stimulation, or TMS, involves rapidly generating a magnetic field outside of the head to induce electrical activity on the cortical surface (Walsh and Cowey, 2000). This is usually done using a handheld TMS coil that can be placed on the surface of the scalp. When the electrical current is switched on the magnetic field is activated – triggering neural activity on the cortical surface (Figure 6.31(a)). This induced activity can either act as a type of 'visual stimulus' itself, or disrupt ongoing visual activity.

6.1.1 Phosphenes and V1 stimulation

When TMS is applied over early visual areas, there are two primary perceptual consequences. One, when people have their eyes closed they tend to experience a weak flash of light, a phosphene. As mentioned above, this is attributed to the activation of visual neurons. The second consequence is that you can experience a visual hole or momentary blind spot – a transient *scotoma* in visual stimulation just after the TMS (Kamitani and Shimojo, 1999).

What is interesting is that the type of phosphene people experience corresponds to the area of cortical tissue stimulated with TMS. For example, when V1 is stimulated, people report smallish static phosphenes. When area MT (the motion area) is stimulated individuals report moving phosphenes (Pascual-Leone and Walsh, 2001)!

These findings taken alone could be viewed as evidence that these areas are responsible for processing of the corresponding visual features (objects, motion, etc.). However, we know that most parts of the brain are joined to most other parts and neural activity can travel very quickly from one location to another; hence, it might be the case that when you stimulate one area activity travels out to multiple other areas. So what if you used TMS stimulation at multiple locations at different times? Might this inform us about neural transmission and neural feedback?

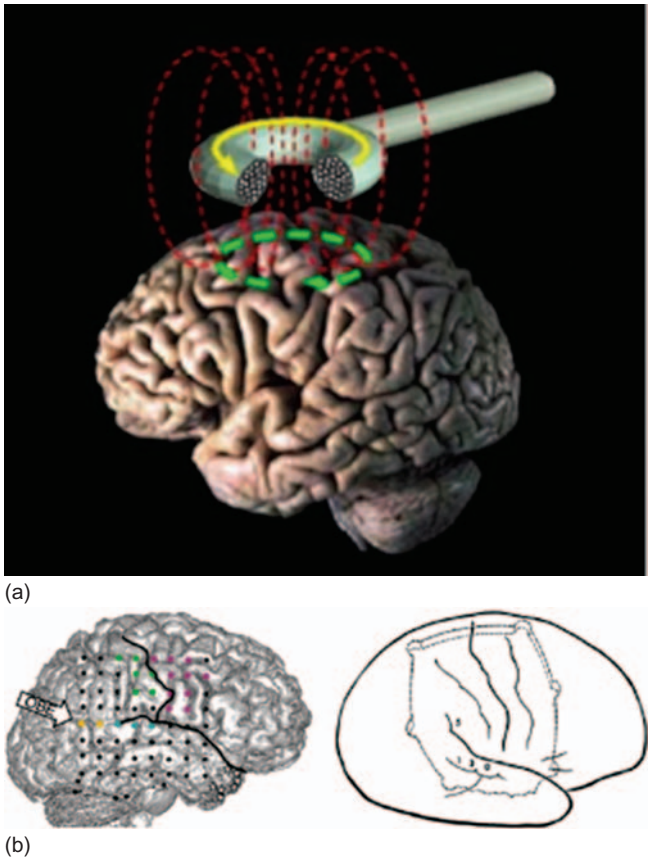


FIGURE 6.31 Stimulating the brain. (a) A transcranial magnetic stimulation (TMS) coil over the brain. The dashed lines show the magnetic field and the area tissue that is primarily affected. TMS is a valuable research tool to investigate the cause-effect relationship between brain activity and visual awareness. (b) When a collection of these electrodes were stimulated the patient reported the experience of looking down at her own body – an 'out of body experience'. *Source*: Blake and Logothetis, 2002.

6.1.2 TMS and cortical feedback

A recent study provided new evidence to support the role of feedback connections in visual awareness (Pascual-Leone and Walsh, 2001). Motion phosphenes were reliably elicited by applying TMS to area MT/V5 (motion areas) and a second TMS pulse was applied to

either V1 or MT at various times before or after the first pulse. Perception of the motion phosphene was selectively impaired when V1 stimulation occurred shortly after MT stimulation (10–40 ms later), but not beforehand. In other words, researchers would first pulse MT, which is higher in the processing hierarchy. Then, at a given time later, they would pulse V1, which is earlier in the stream of processing. When this was done at the right time interval, subjects no longer perceived the phosphenes. This suggests that feedback projections from MT to V1 might be necessary for conscious perception of the phosphenes. The authors concluded that MT activity *alone* might be insufficient to support awareness of motion and that feedback activity to V1 may be necessary for visual awareness. These findings provide support for the interactive theory of visual awareness.

A TMS study of a blindsight patient, GY (remember that patients with blindsight typically have a large section of V1 damaged), provides some evidence in favor of the feedback re-entrant model of visual awareness (Cowey and Walsh, 2000). In GY, stimulation of MT elicited motion phosphenes only when applied to the hemisphere housing the intact V1, but not on the side with damaged V1 cortex. So even though area MT was perfectly fine in both cortical hemispheres, stimulating MT on the same side of the head as the damaged V1 did not lead to the perception of phosphenes. In contrast, motion phosphenes were successfully elicited in all normal subjects tested as well as in a retinally blind patient. Further tests of the interactive model should pursue whether direct cortical stimulation of extrastriate areas can elicit phosphenes in patients with V1 damage.

Another fascinating example of the modulation of visual awareness comes from a study in which researchers directly stimulated neurons in a monkey's brain (Salzman *et al*., 1990). As we mentioned earlier, neurons in cortical area MT respond selectively to particular directions of motion and neurons that prefer similar directions tend to be clustered in cortical columns. In other words, a select bunch of neurons in MT might only be vigorously active when a monkey is presented with rightward motion. In this experiment, researchers directly stimulated some of these direction-selective neurons in the monkey's area MT. They did this while the animal was viewing ambiguous dots moving in many possible directions, while performing a motion discrimination task. This microstimulation biased the animal's judgments toward the direction of motion that the stimulated neurons typically respond to. In other words, it was as if stimulating these neurons led to a stronger perception of that particular motion direction, enough to shift the monkey's impression of motion a fair bit, if the motion in the stimulus was quite ambiguous.

Much more complex perceptual experiences may be triggered by neural stimulation, even what might be called *out-of-body experiences*. An epilepsy patient who (due to the severity of her condition) had electrodes temporarily implanted in her brain reported such experiences. When two specific electrodes were stimulated over the temporal parietal junction (see Figure 6.31(b)), she reported the novel sensation of falling or floating (Blanke *et al*., 2002). She described the sensation as 'falling from a height'. Stronger stimulation led to a report of an apparent out-of-body experience. That's right, she claimed actually to experience seeing her body from above, lying in bed. However, she did not see her own face, only from her trunk downwards. This finding is important because the angle she reported seeing her body from was different from what she normally experienced. So, this suggests that familiar experiences (her normal body view) can be combined to form novel experiences of seeing her own body from different angles. This concept has exciting implications for the study of perceptual experience, because it suggests that experiences of an internal origin do not simply have to be a repeat of previous perceptual phenomena.

Stimulation studies allow scientists to pin down the cause-effect relationships between neural activity and perceptual experiences and can therefore reveal what brain areas are responsible for what we see. In essence, it is like taking control of the brain. By directly stimulating the cortex and bypassing sensory organs, such as the retina, it may be possible to identify which brain areas are more directly linked to perceptual experience.

6.2 Unconscious perception

How can something be both unconscious and still be called perception? Wouldn't the fact that you're not aware of something suggest that your brain was unable to process or identify that stimulus? In the current context, we use the term *unconscious perception* to refer to situations when subjects report not seeing a given stimulus, but their behavior or brain activity suggests that specific information about the unperceived stimulus was indeed processed by the brain. Neural activity does not always lead to awareness. Neurons may fire in a stimulus-specific way at many levels of the brain, but this activity may not be strong enough, last long enough, or involve enough neurons or brain areas to lead to awareness. One of the best examples of this comes from neural recordings in animals under anesthesia; visual neurons

in many brain areas still show strong stimulus-selective responses. In this section, we will learn that even when a person is fully awake and alert, unconscious visual processing can also occur in many situations.

In a previous section, you learned about how 'what you see is what you get activated' during binocular rivalry. In other words, if you become conscious of a particular stimulus, then neurons in your brain that represent that pattern will become highly active. However, here we will learn that the opposite is not necessarily true. If you have some activity in a given brain area, this does not mean you will necessarily perceive the stimulus. Without *enough* activity in the *right* brain areas, awareness may simply fail: the result is unconscious perception.

When two different stimuli are flashed briefly enough in quick succession, the visual system can no longer separate the two stimuli. Instead, what people perceive is a mix, or a fused blend of the two images. For example, if we were to expose you to a red square, then quickly follow it with a green square, what you might experience is a combination of the two – a yellow square. This method can be used to present invisible patterns, such as a face or a house, by flashing red contours on a green background to one eye and the opposite colors to the other eye (Figure 6.32). When subjects were presented with such images in the fMRI scanner, the fusiform face area responded more strongly to faces and the parahippocampal place area responded more to houses, even though subjects were not aware of the images (Moutoussis and Zeki, 2002). This is an example of unconscious perception. The activity in ventral temporal parts of the brain could differentiate, to some degree, whether a face or house was presented, even though the subject could not verbally report a difference. So just because an area is somewhat active does not mean we will be aware of what that brain area represents. Perhaps this level of activity is just not enough. Stronger responses were found in these brain areas when just a single red-green pattern was shown so it was clearly visible.

Area MT, a brain area specialized for processing motion, also responds to unperceived motion. When a moving stimulus is presented far out in the periphery of the visual field and is crowded by other stimuli, area MT still responds to motion – even when subjects are not aware of the motion (Moutoussis and Zeki, 2006). In this experiment, the motion stimulus was flanked on two sides by flickering stimuli, making the visual space so busy and cluttered that subjects could not see the motion in the display. Although MT responded somewhat to the perceived motion stimulus, it responded much more strongly when the surrounding flickering stimuli were removed and the motion stimulus was clearly perceived.

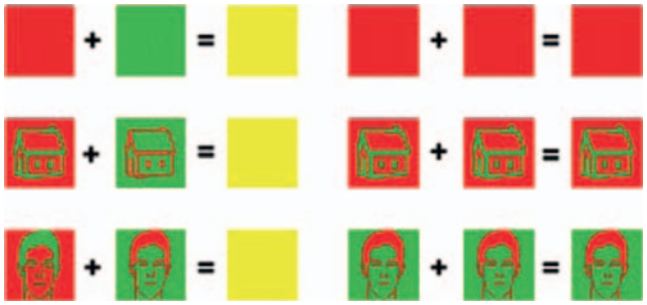


FIGURE 6.32 Red + green = yellow. The red and green combine to form the yellow square of color. Hence, the images of the house and face become invisible when briefly shown one to each eye. However, the brain still responds to these unseen patterns. *Source*: Moutoussis and Zeki, 2002.

In other studies, researchers used binocular rivalry (which we discussed in an earlier section) to render pictures of fearful faces invisible (Figure 6.33(a)). The expressions of the faces carried emotional content, although the subjects were never aware of seeing the faces. The amygdala, a brain region in the medial temporal lobe that normally responds to emotional stimuli, also responded to the invisible fearful faces (Pasley *et al*., 2004). Figure 6.33(b) is a plot of the activity in the amygdala; the red line represents the response of the amygdala to the emotional face images.

It is clear that many brain areas may continue to show stimuli-specific activity despite the fact that we are unaware of that stimulus. One thing this suggests is that even if a brain area is processing a stimulus, this doesn't mean we will *perceive* that stimulus. If neural activity in a given area is not enough to result in awareness, then what is? In most of these studies, greater activity was found when subjects were aware of a stimulus than when they were not, suggesting that a minimum level of activity may be needed to make the difference between no awareness and awareness. A low level of neural activity below a specific *threshold* might not be adequate to result in being aware of a stimulus.

This idea of a neural threshold for visual awareness fits nicely into both the hierarchical and interactive models of visual awareness we discussed earlier. For the hierarchical model, an adequate level of neural activity would have to be maintained in high-level visual areas for awareness to occur. For the interactive model, feedback signals might act to boost neural activity at each level of processing, leading to activity that surpasses the threshold for visual awareness in multiple brain areas. In sum, we can conclude that at least two things are needed for visual awareness:

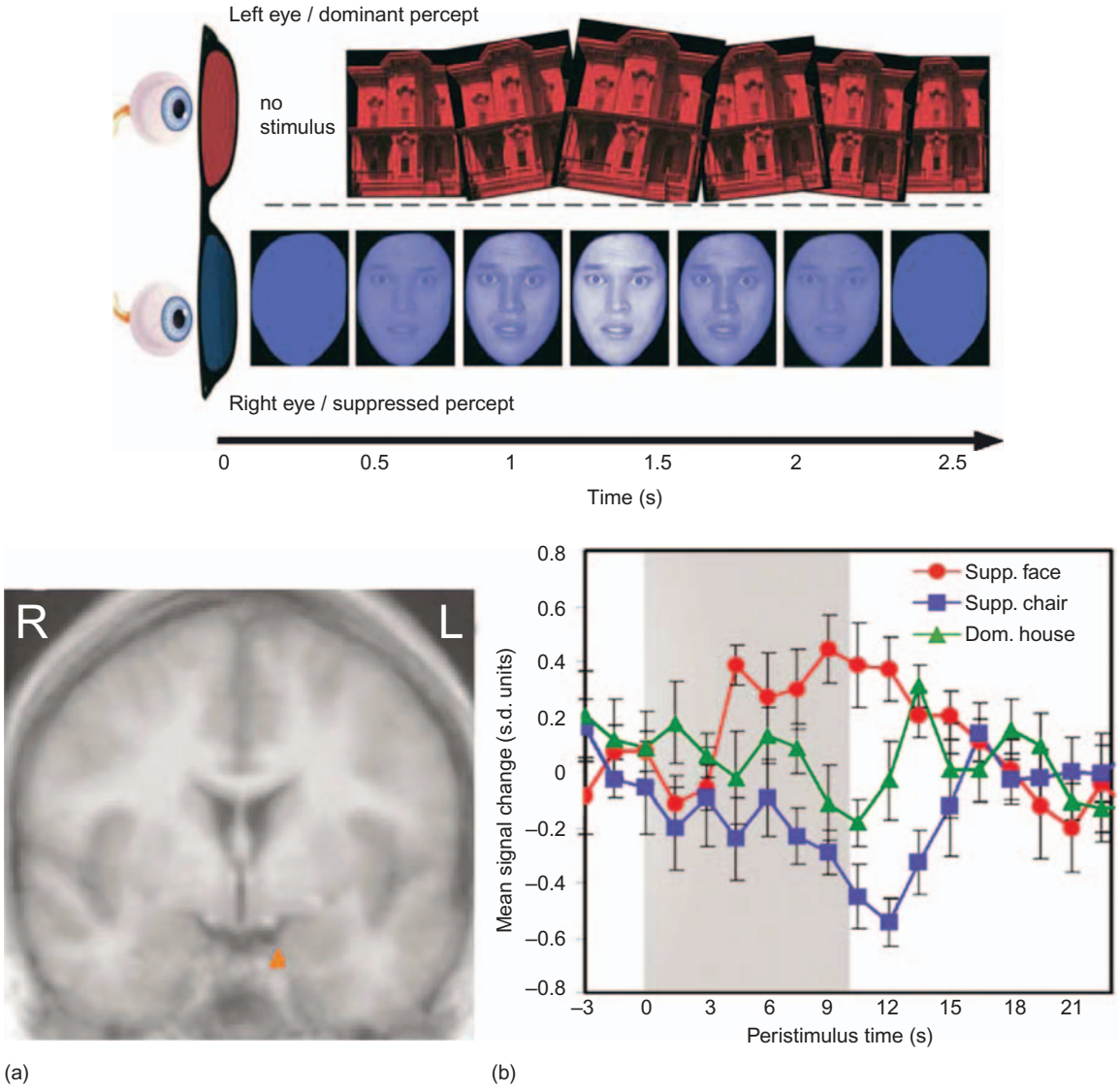


FIGURE 6.33 The emotion is still perceived but not the face. (a) Schematic of the stimulus used in the Pasley *et al.* (2004) study. The red building presented to the left eye suppresses the face in the right eye out of awareness, as in binocular rivalry. The faces have emotional expressions. (b) This graph shows the activity in the amygdala (an emotional response area of the brain). The red plot shows that the activity in the amygdala increases when emotional faces are presented, even though they are out of awareness. The brain cannot see the face, but it can detect the emotion. *Source*: Pasley *et al.*, 2004.

(1) activity in the right neurons or brain areas and (2) activity that exceeds a critical threshold. Further research may show which of these models best describes the brain basis of visual awareness.

7.0 SUMMARY

Vision is perhaps our most important sense modality. It is certainly the one that has seen the most research. Over the past decade or so, scientists have learned a great deal about the neural correlates of conscious and unconscious perception and how the disruption of different brain areas can disrupt specific aspects of visual consciousness. A consistent finding is that primary visual cortex seems to be important for the ability to perceive any visual feature at all, while higher brain areas may be important for perceiving *particular* visual features or objects. Current evidence provides support for both hierarchical and interactive theories of visual awareness. Future studies will improve our understanding of how the brain gives rise to our subjective visual experiences.

In this chapter, we traced the functional properties of neurons as visual signals travel up from the retina to the primary visual cortex and onward to higher areas in the dorsal and ventral visual pathways. Progressing up the visual pathway, receptive fields gradually become larger and respond to more complex stimuli, following the hierarchical organization of the visual system.

V1 is selective for many visual features, including orientation, motion, and binocular disparity. Damage to V1 can severely impair or eliminate conscious vision, although remaining activity in extrastriate areas may support the ability to detect visual events even without being visually conscious, the condition called blindsight. Extrastriate visual areas (the ones outside of V1) seem to be important for perceiving specific visual features: area V4 is important for color perception and area MT for motion perception. Damage to these areas may lead to selective impairment in the perception of these higher-level features of the visual world.

According to the hierarchical theory, higher extrastriate areas are closely linked to visual awareness whereas V1 is not. In contrast, the interactive theory emphasizes that feedback signals to V1 may be important for awareness. Current evidence provides support for both theories.

Damage to the dorsal pathway can lead to *optic ataxia* (impairments in visually guided actions) or *visual neglect*. Damage to the ventral temporal cortex can lead to impairments in visual perception, object recognition or face recognition. Patients with brain injuries in the ventral and dorsal pathways reveal a dissociation between the conscious perception of basic shapes and orientations and the ability to perform visually guided actions.

In the ventral temporal cortex, some brain regions, such as area LOC, seem to have a general role in object recognition, while other areas, such as the fusiform face area and parahippocampal place area, appear to have more specialized roles. Many studies show that activity in these areas is strongly associated with the conscious perception of objects. Nonetheless, evidence of unconscious processing can be found in many brain areas, including high-level object areas.

8.0 STUDY QUESTIONS AND DRAWING EXERCISES

1 For the brain drawing in Figure 6.34:
   a Copy the brain figure. Which way is it facing?
   b Identify the visual regions (labeled) and some of the things they do.
   c Can you color in the dorsal and ventral streams? What is the difference between their functions?
2 In Figure 6.35, can you describe what is happening in your own words? What is the cat seeing? Which visual areas are likely to be involved? What kind of neural mechanisms improve the ability of the cat to perceive contrasts and boundaries?

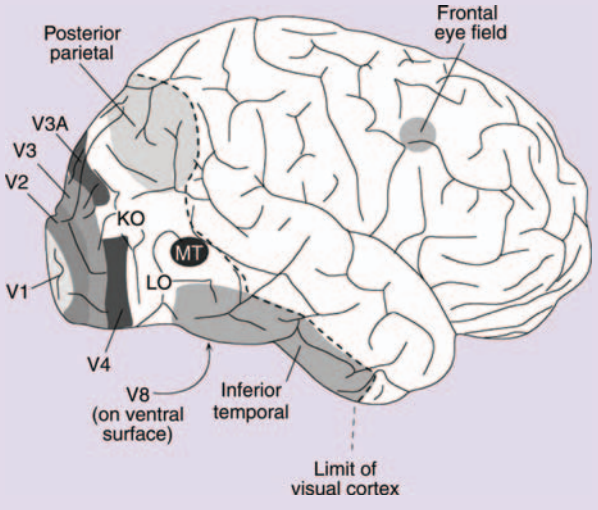


FIGURE 6.34 Visual areas of the human cortex. *Source*: Rosa, 2002.

3 For Figure 6.36:
   a Draw each figure in color.
   b What can we learn from (a)? What parts of the visual cortex are likely to be involved?
   c How about (b)? Are different parts of the visual cortex likely to be involved than in (a)?
   d For the third image in the figure, what does the subject in the experiment perceive? Why do the colors look mixed together? What is the purpose of this experiment and what are the results?
4 A question to think about: how can we compare conscious and unconscious visual stimuli?

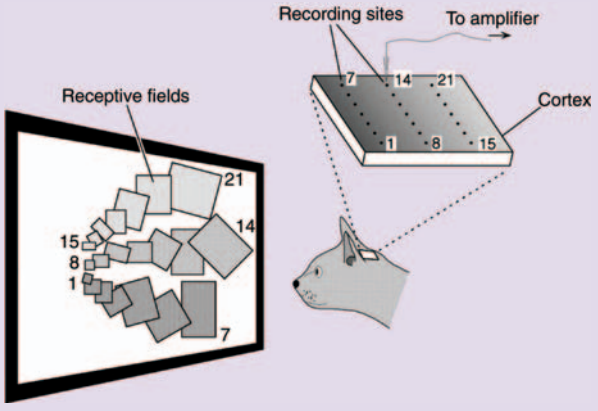


FIGURE 6.35 Recording from the brain of a cat. *Source*: Rosa, 2002.

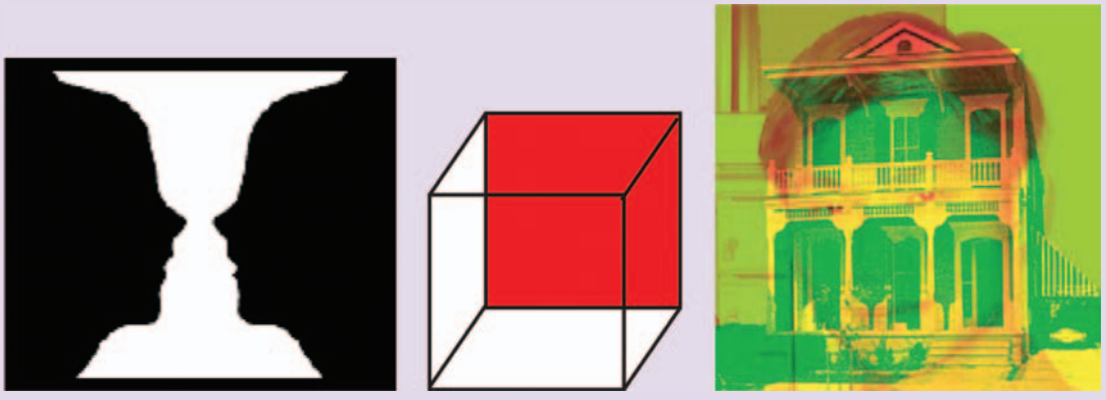
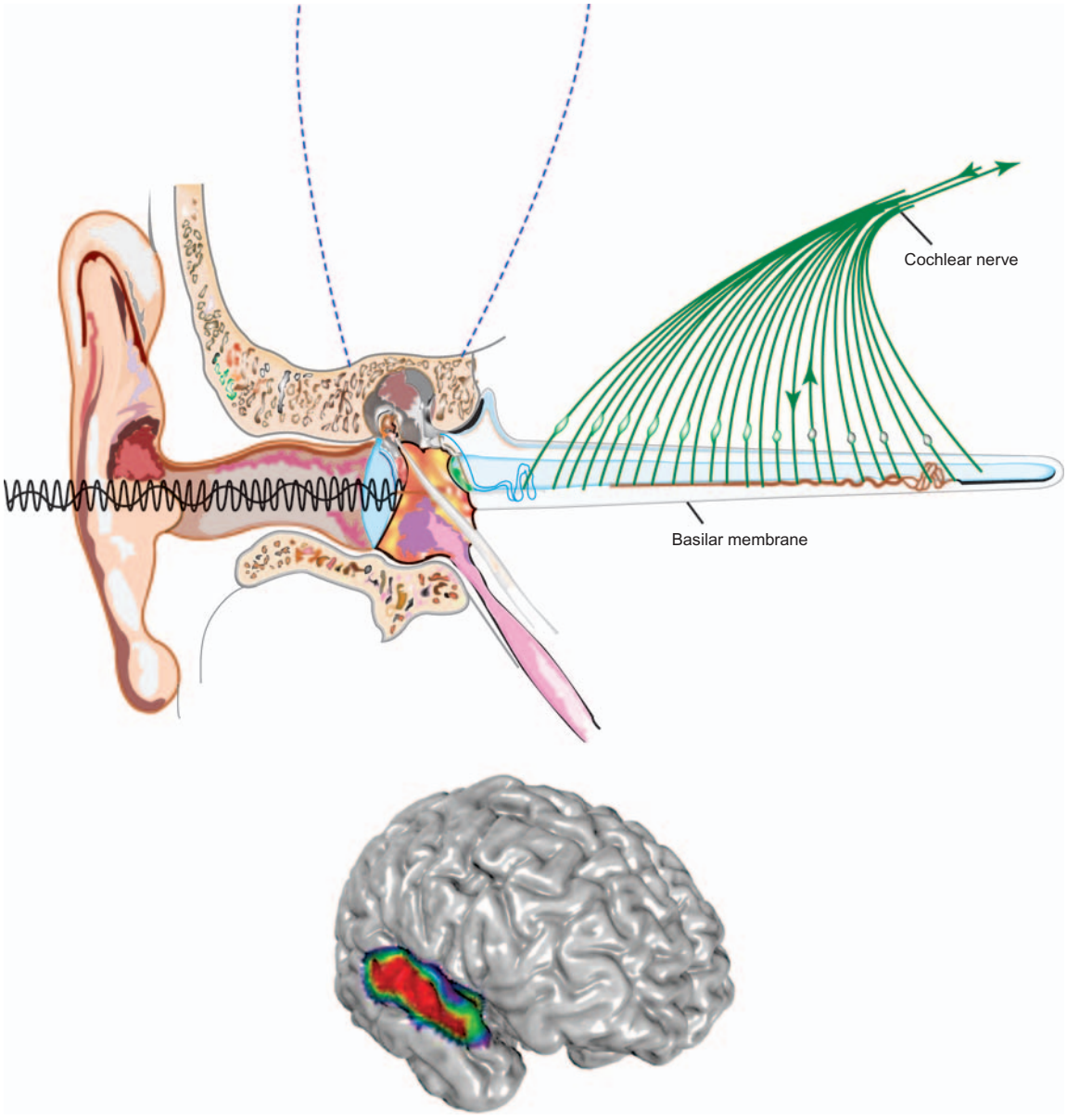


FIGURE 6.36 Visual ambiguities. *Source*: Kim and Blake, 2005.

It was very fortunate that, even in Helmholtz's time, the great anatomical discoveries by Corti (and others) had already made it clear that the vibrating tissue most important for hearing is the basilar membrane of the inner ear, because the cells on which the nerve endings terminate are seated on this membrane … the problem of how we hear was reduced largely to a mechanical question: how does the basilar membrane vibrate when the eardrum is exposed to a sinusoidal sound pressure?

Bekesy, Nobel Prize Lecture (online)



The auditory system really starts deep inside the ear canal at the eardrum. Air vibrations, which are fast compressions and expansions of the air, vibrate the eardrum, which transmits mechanical vibrations that end up triggering receptors (hair cells) located on the basilar membrane. Axons from the receptor cells combine to make up the auditory nerve, which goes through several stages of processing before reaching cortex. The auditory system is extraordinarily sensitive, able to pick up even the sound of air molecules in very quiet environments. *Sources: Top*: Standring, 2005; *bottom*: Ramachandran, 2002.

CHAPTER

7

Hearing and speech

OUTLINE

1.0 INTRODUCTION

This chapter provides an overview of how we hear – from simple sounds, to complex speech, to symphonies. We begin with basic information about how we process sounds: from the ear, through the ascending auditory pathways, to auditory cortex. Next, we discuss specific types of sound processing such as speech and music perception. As you can imagine, sound perception changes throughout life, for example, as we acquire speech and language as infants and young children. You might have an intuition – and you would be correct! – that the neural systems underlying sound processing may be set up somewhat differently for people who are skilled musicians or for linguists who speak several languages fluently. Therefore, we will discuss the effects of learning and expertise on

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

brain systems for sound processing and how they differ throughout life and across individuals. But sound processing does not happen in isolation – what we hear combines with what we see and touch, as well as with our stored memories and experiences.

1.1 A model for sound processing

Our environment is frequently quite noisy with many types of sounds reaching our ears at the same time. Think about a large college classroom before a lecture begins: there are the sounds of students' voices, chairs scraping, doors opening and closing, backpacks being unzipped, books being dropped onto desktops. All of these sounds hit our ears at the same time and yet we have little difficulty in perceiving them as separate events or auditory 'objects'. This process is called *auditory scene analysis* and forms the basis for understanding how the auditory system decodes a complex listening environment (Bregman, 1990). In this chapter, we will discuss how the auditory system decodes this type of auditory scene. We will begin, however, with a functional framework with which to understand the processes of the auditory system and how they interact with other subcortical and cortical systems.

1.1.1 A working framework for sound perception

In Chapter 2, we discussed a modal model for understanding brain processing. The same general concepts hold for auditory processing: sensory (sound) inputs enter the system and there is a very brief storage (echoic memory) for these inputs (Figure 7.1). Selective attention allows the system to direct its attention to a subset of the inputs for further processing. At this stage, there are complex interactions between the new inputs and existing memory and experiences, as well as with other sensory systems. The ultimate goal or 'action' to be performed is important as well and will affect how information is encoded and stored. It is important to note that this model for auditory processing is not a one-way process, with sounds being decoded, understood, and then stored into long-term memory. There are interactions that occur throughout the encoding of sounds, both within the auditory system itself and across other sensory, cognitive, memory,

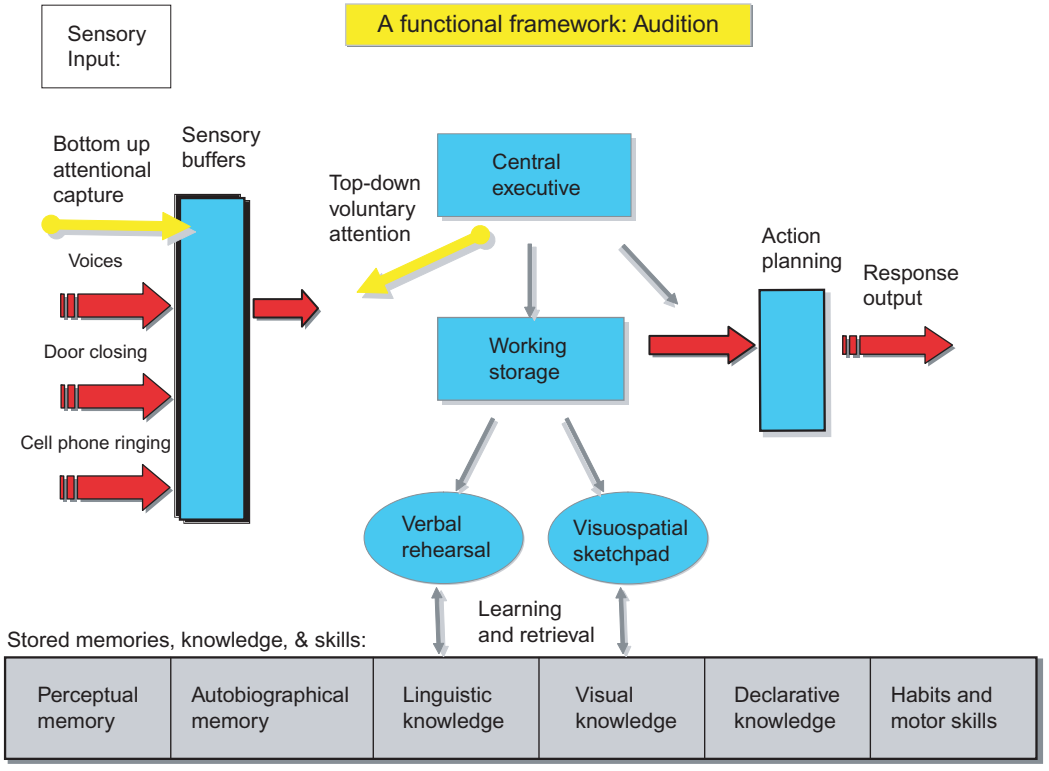


FIGURE 7.1 A functional framework for auditory processing, adapted from the general functional framework presented in Chapter 2. Sensory inputs, such as the sound of someone's voice or a cell phone ring, enter the system (see red arrows on the left side of the figure). There are early influences from bottom-up and top-down attentional processes (yellow arrows). These inputs make contact with working storage, long-term knowledge, and action systems. It is important to keep in mind that the processes underlying auditory function are highly interactive, with feedforward, feedback, and integrative processes.

and motor systems. The anatomy and connectivity of the auditory system reflects this complexity, with multiple stages of processing and neural pathways, including the ascending pathways from the ear to the brain, descending pathways that carry information back to the peripheral system, and many parallel pathways within brain regions and across the two hemispheres.

1.1.2 Limited and large capacity

As we discussed in Chapter 1, brain processes have both limited and large capacity aspects: this is the case for the auditory system. There are some specific limitations in decoding sound inputs. For example, if you present speech through headphones, it is easy to attend to each word uttered. However, if two different speech streams are presented to the two ears, it becomes a very difficult task to try to attend to each stream. In fact, we selectively listen to one stream or the other (Broadbent, 1982). Thus, there are some limits to the capacity for decoding complex sounds entering the auditory system and a role for central executive function in directing attention selectively to some of the sounds in a complex listening environment. On the other hand, our capacity for learning new sounds or auditory objects (such as spoken words) continues throughout life and appears to be virtually unlimited in capacity. In fact, an average adult's vocabulary is estimated at more than 100,000 words. The same is true for recognizing new melodies and the voices of new friends and acquaintances. Therefore, while some capacity limits exist in attending to sounds during perception and encoding, once learned there appear to be virtually no limits regarding the capacity to remember new sound-based items.

1.1.3 Orders of magnitude and levels of analysis

As in other brain systems, auditory processing contains processing units that comprise many orders of magnitude from individual hair cells at the periphery, to single neurons in auditory cortex, to large-scale neural networks in the auditory language system. The auditory system has been studied at each of these levels of analysis in both human and in animal. In this chapter, we will include information that we have learned at each of these levels of analysis. However, a large focus of the evidence presented in this chapter will be on what we have learned about auditory processing at the system level from neuroimaging – positron emission tomography (PET), magnetic resonance imaging (MRI), functional MRI (fMRI), magnetoencephalography (MEG), and electroencephalography (EEG) – studies. The advent of non-invasive measures to investigate cortical processing has revolutionized the field of cognitive neuroscience and psychology in general. Previously, we relied on data from animal studies, made inferences from behavioral and psychophysical studies with healthy individuals, or investigated sound and language processing in humans who had suffered brain damage due to injury, disease, or stroke. The capability of investigating brain processes in healthy individuals has provided us with a wealth of new information about sound and language processing. It has also provided us with the ability to investigate brainwide processes in large-scale systems that span multiple brain regions, such as the language system.

1.1.4 Time

Time is a critical aspect of auditory processing: the auditory system differs from the visual system in that all sound processing occurs over time. Nothing 'stands still' in sound processing. Speech, the most complex signal that the auditory system must decode, has differences in speech sounds (phonemes) such as /b/ and /p/ that occur on a scale of 20–30 thousandths of a second (milliseconds), and yet our speech perceptual processes decode these transient differences with ease, even in relatively noisy environments (Gage *et al.*, 1998, 2002).

Thus, the speech decoding system has a high temporal resolution of fine-grained and transient changes at the level of the phoneme. However, the speech system also needs to decode information that changes over a longer time span than those contained within phonemes: syllabic stress (such as the different pronunciation of 'melody' and 'melodic') is an important speech cue and occurs in a time window of approximately 200 ms. Other key information occurs over 1–2 seconds (1000–2000 ms) at the level of a sentence, such as the rising intonation that is associated with asking a question. Thus, each of these time windows – 20, 200, 2000 ms – is critical to the accurate decoding of speech and information extracted from each of these decoding processes must be available for integration in the complex processes underlying the mapping of sound onto meaning (Figure 7.2).

Before we begin our discussion of how the brain processes complicated listening environments, with human voices, complex environmental sounds, music, we need to discuss some basic principles of sound and hearing. We will begin with the physical features of sounds and how these features correspond to psychological aspects of sounds. Next, we will step through the processes and stages of peripheral hearing and subcortical feature extraction.

1.2 Sound and hearing basics

1.2.1 Physical features of sounds

How does the human auditory system transform sounds into comprehensible speech or recognizable melodies? Let's begin with how we encode simple sounds at the level of the ear. A physical definition of sound is the vibration that occurs when an object moves in space, producing an audible sound. What we hear is not the vibration itself but the effects of vibration in sound waves that move, or propagate, through space and make contact with our ears. The sinusoid (Figure 7.3) is a basic building block of sound that has three main physical aspects: frequency, intensity and time. The frequency of a sound is the rate of sound wave vibration and is measured as cycles completed per second, or *hertz* (Hz). A sinusoid with 1000 cycles per second has the frequency of 1000 Hz. The human auditory system can detect sounds across a wide range of frequencies, estimated at 20 to 20,000 Hz.

The intensity of a sinusoid reflects the amplitude (or displacement) of the wave within its cycle and over time. In Figure 7.3 (left panel), we show a 1000 Hz sinusoidal tone in the time domain, with time on the x-axis and intensity on the y-axis. On the right panel of Figure 7.3, we show the same tone in the frequency domain, with the frequency (Hz, or cycles per second) on the y-axis and time on the x-axis. Note that the spectral energy of a sinusoidal tone is limited to a single narrow band, so a 1000 Hz tone has energy centered only at 1000 Hz. This is why a sinusoidal tone is frequently referred to as a 'pure' tone.

Of course, most sounds that we hear are more complex than a pure tone. A piano chord, a car horn honking, a person's voice, all have complicated structures. How do we describe these complex sounds in terms of the three physical parameters of frequency, intensity, and time? Joseph Fourier (1768–1830), a Frenchman who lived in the Napoleon I era, developed a series of theorems that describe how even complex signals can be separated into a series of simpler constituent parts

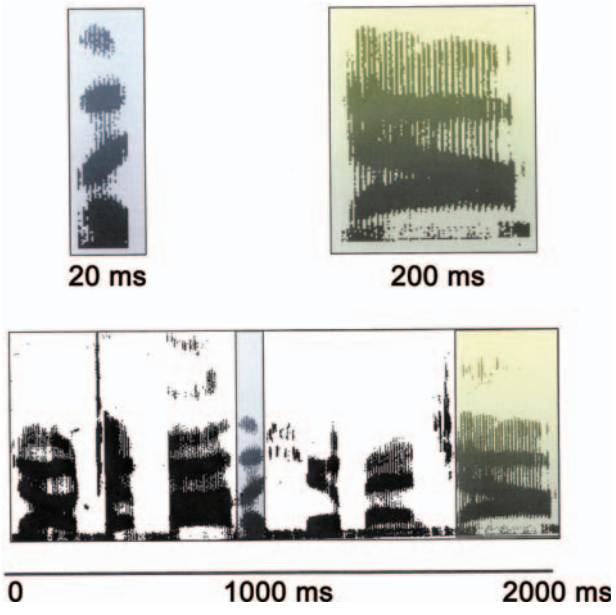


FIGURE 7.2 A spectrogram is a picture of the sound-based features in speech. Time is represented on the x-axis and frequency is represented on the y-axis. The darker shading represents higher intensity. Speech contains harmonic content (formants) at specific regions in the spectral (frequency based) aspect of the spectrogram. Here we show a spectrogram showing three time scales critical for decoding speech. *Upper left*: Detail of the transients at the onset of a consonant, with transitions that occur on a time scale of ~20 ms. *Upper right*: Detail of the formants in a syllable which occurs on a time of ~200 ms. *Bottom*: A sentence that occurs on a time scale of ~2000 ms.

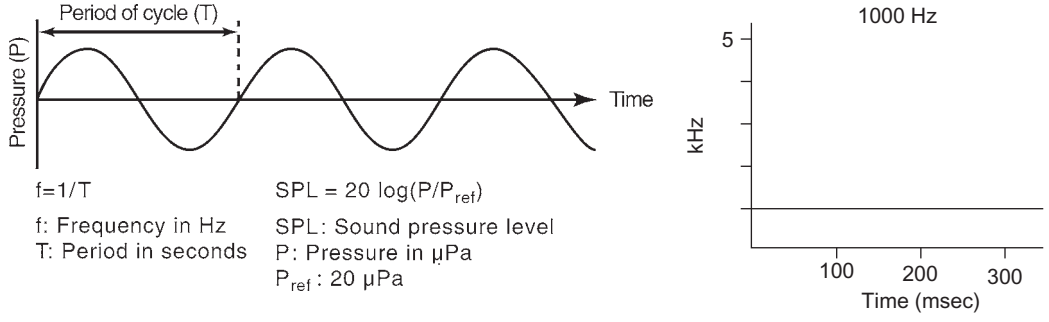


FIGURE 7.3 Left panel shows a sinusoidal tone. Time is represented on the x-axis, amplitude is shown on the y-axis. The frequency of the sinusoid is based upon the number of cycles per second; thus a 1000 Hz tone has 1000 cycles per second. Right panel shows the same sinusoidal tone with its frequency focused on 1000 Hz. Sinusoidal tones have a single frequency, which is why they are referred to as 'pure' tones. Most sounds we hear are spread over multiple frequency bands. *Sources*: *Left*: Brown, 2003; *right*: Boatman, 2006.

through what is now called a *Fourier analysis* (Fourier, 1822). The work of Fourier was advanced by Georg Ohm (1789–1854), who proposed that the separation of complex sounds into simpler sinusoids occurred at the ear in hearing.

While we have mentioned the frequency, intensity, and time of a sound as comprising the basic physical features, sounds have other qualitative aspects. For example, if you heard someone play middle C (~261 Hz) on a piano while at the same time an oboist played middle C, could you tell these sounds apart in spite of the fact that they are of identical frequency? Of course you could easily do so, suggesting that there must be many more dimensions in sound quality than just frequency. In this example, the *timbre* or quality of the note helps us distinguish between musical instruments, even when the notes they produce are identical in frequency. Timbre also allows us to distinguish human voices.

1.2.2 A scale for sound intensity

The dynamic range of the human hearing system is extremely broad: we can hear barely perceptible sounds of very low intensity and very loud sounds that actually cause pain. This range has been calculated as ranging from 1 unit of intensity to 1,000,000,000,000,000 (10^{15}) units. This range is so large that it is difficult to deal with using normal numbering schemes. We typically use a logarithmic scale in order to deal more easily with the huge range in units of intensity, the *decibel* (dB) system. The dB scale is a relative (not absolute) scale and is based upon the ratio of two quantities: the relative intensity of a sound based on either the sound pressure level (SPL) in the air where hearing is occurring, or based upon the hearing threshold or sensation level (SL) of an individual. (Note: there are many other ratios used in describing hearing. We use SPL and SL here because they are common ratios used to describe sound intensity.) Human hearing ranges from ~1 (threshold) to 150 dB SPL (Figure 7.4).

1.2.3 Psychological aspects of sounds

While sounds have physical parameters (frequency, intensity, time) that can be measured with a fine degree of accuracy, how do we know how they are perceived? The physical parameter of frequency, or cycles per second, corresponds to the psychological or perceptual quality of *pitch*. Pitch is a subjective perception, usually

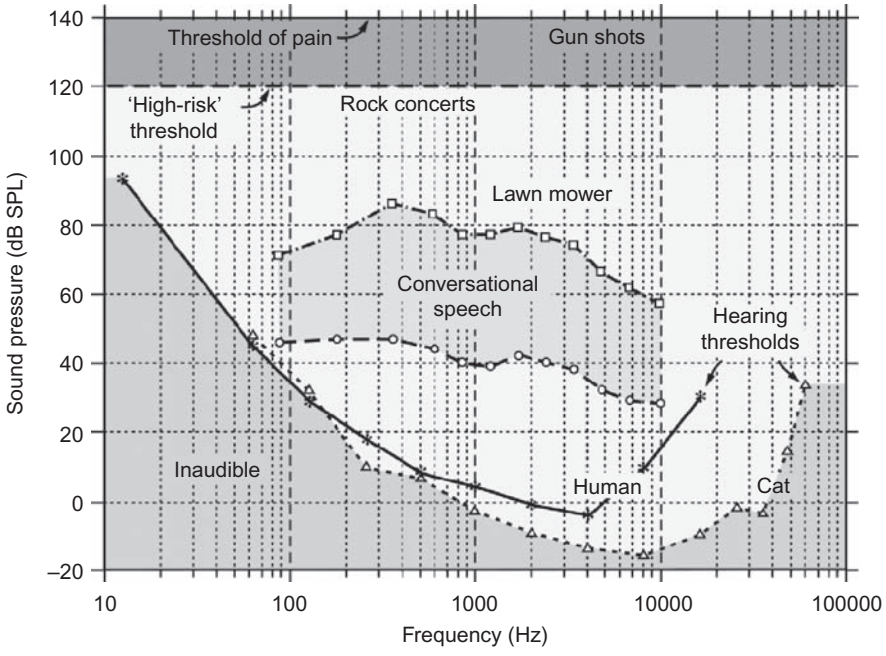


FIGURE 7.4 Hearing threshold and range of hearing for human listeners. Shown also are the ranges of frequency and sound pressure levels of common environmental sounds, including human speech. The most intense sounds are capable of damaging the inner ear receptor organ. The hearing sensitivity of the cat, a laboratory animal commonly used in studies of the peripheral and central auditory system, is illustrated as well. *Source*: Adapted with permission from Brugge and Howard, 2002.

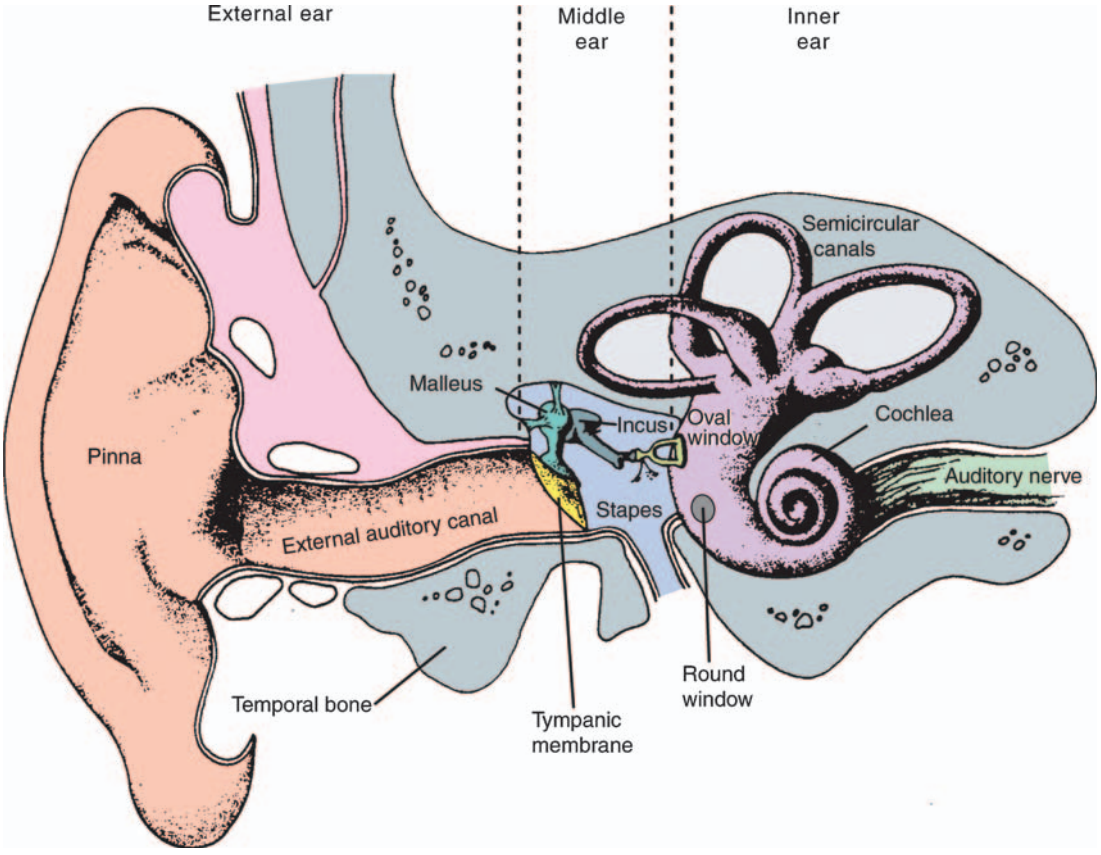


FIGURE 7.5 Drawing of the auditory periphery within the human head. The external ear (pinna and external auditory canal) and the middle ear (tympanic membrane or eardrum, and the three middle ear ossicles: malleus, incus, and stapes) are indicated. Also shown is the inner ear, which includes the cochlea of the auditory system and the semicircular canals of the vestibular system. There are two cochlear windows: oval and round. The oval window is the window through which the stapes conveys sound vibrations to the inner ear fluids. *Source*: Brown, 2003.

described as the 'highness' or 'lowness' of a sound, for example, the pitch of a person's voice or of a note on a piano. We use the physical and psychological terms differently when discussing sound perception. Here's why: while we may know the frequency of a sound because we have measured the cycles per second, we do not know the precise pitch that an individual experiences. A highly trained opera singer, for example, may have a very different sense of the differences in pitch between closely matched sounds than an untrained individual, even though both have normal hearing. This is also the case for the physical parameter of intensity, which corresponds to the subjective perception of *loudness*. Individual listeners have a wide variety in how they perceive the loudness of sounds, depending on many factors ranging from hearing loss to personal preference. Therefore, it is important when describing sounds to be aware if you are describing the *measured* physical parameters or the *subjective* psychological features.

1.2.4 From the eardrum to the auditory nerve

As we mentioned above, we will step through the stages of hearing and subcortical feature extraction processes as sounds are transmitted to auditory cortex. You will see that there are complex mechanisms at work, even in decoding relatively simple sounds in a quiet environment. Let's begin with how sounds proceed from vibrations at the eardrum, through the fluid of the inner ear, to innervate fibers at the auditory brainstem on their way to auditory cortex.

Vibrating objects cause sound waves to move through air. When these sound waves reach the tympanic membrane, or eardrum, they propagate through

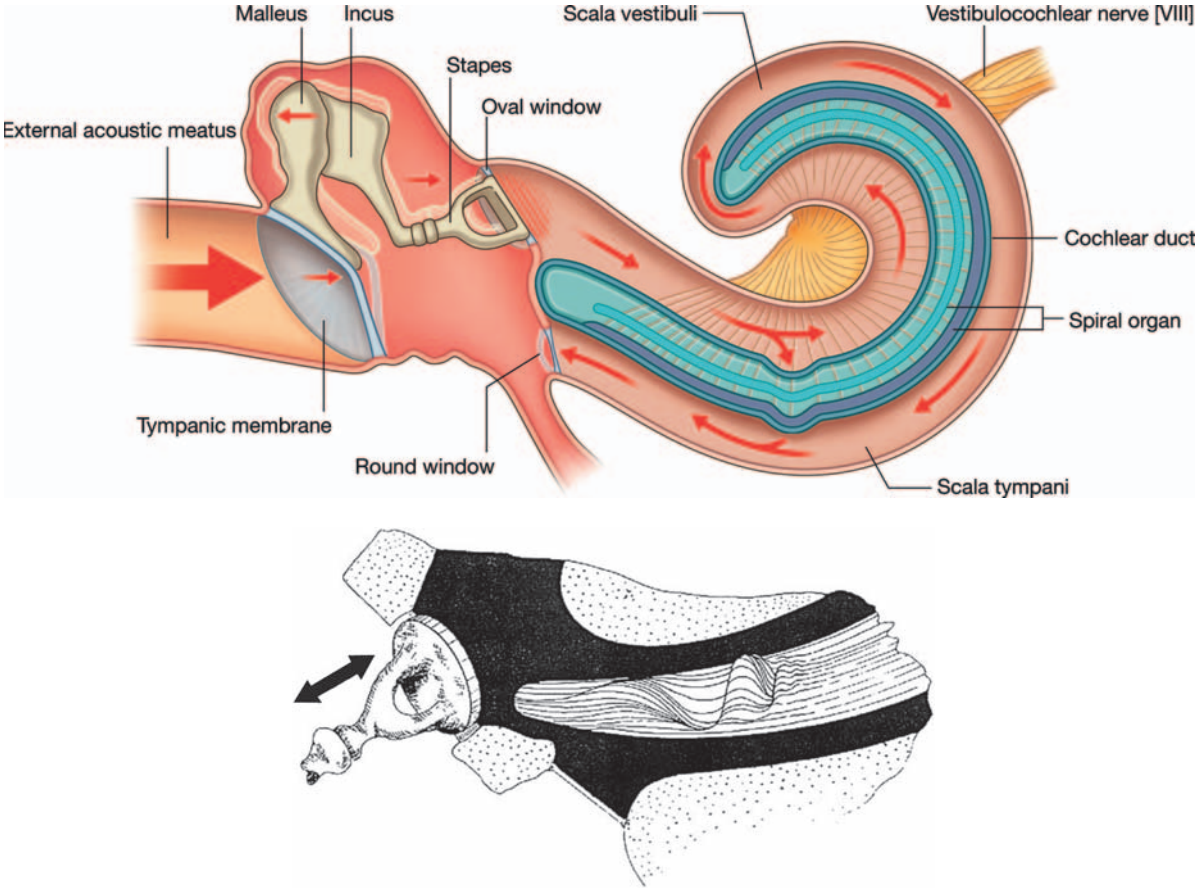


FIGURE 7.6 *Upper* panel depicts the transmission of sound, with a perspective view of the cochlea showing the basilar membrane. Note that the red arrows depict sound transmission and are bidirectional. *Lower* panel depicts a traveling wave of sound as it crosses the basilar membrane. The wave is shown as frozen in time and somewhat exaggerated in order to illustrate the movement across the basilar membrane by sound. *Sources*: *Top*: Drake, 2005; *bottom*: Javel, 2003.

the middle ear through the mechanical action of the three bones of the middle ear: the hammer, anvil, and stirrup, to the cochlea, the organ of hearing in the inner ear (Figure 7.5) (for more on hearing fundamentals, see Moore, 1995).

At the stage of the *cochlea*, in the inner ear, the physical aspects of the sounds are encoded. (See Figure 7.6, upper panel, for a perspective of the cochlea showing the shape of the *basilar membrane*.) The traveling wave of sound moves across the basilar membrane from the base to the apex (Figure 7.6, lower panel). The basilar membrane is topographically organized in a frequency-specific manner, called *tonotopy*, with higher frequencies encoded at the base and lower frequencies encoded at the apex.

How is the traveling wave converted to a neural code and transmitted to the brain? Within the cochlea, there are approximately 16,000 sensory receptors called the *hair cells*. The motion of the traveling wave along the basilar membrane sets the tiny hair cells into motion. The peak amplitude of the traveling wave causes maximal bending of the hair cells located in specific regions or places of the basilar membrane, thus encoding the frequency of sounds. This is called the *place principle* of hearing and is based on the theory that the brain decodes the frequencies heard based upon which hair cells along the basilar membrane are activated.

At this stage of processing, the movement of the hair cells produced by the traveling wave of sound is transformed or transduced into electrical responses in fibers of the *auditory nerve* (Kelly *et al*., 1996). Specific hair cells map onto to specific fibers in the auditory nerve and these fibers have a *characteristic frequency* to which they are most sensitive.

The fine mapping of hair cells onto auditory nerve fibers preserves the frequency information in the sound as it is converted from vibration at the eardrum, to mechanical movement in the middle ear, to traveling

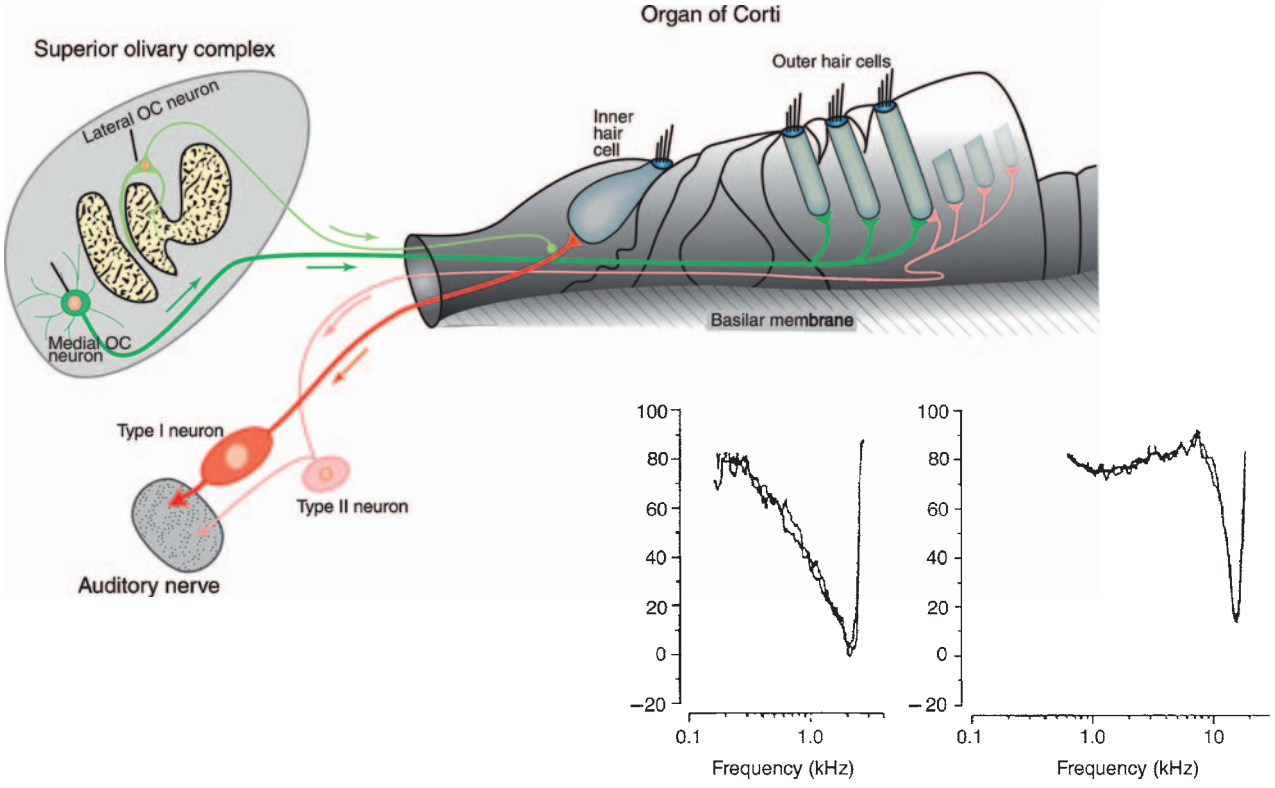


FIGURE 7.7 Top panel depicts innervation patterns of afferent and efferent neurons in the organ of Corti, located within the cochlea (see Figure 7.6). Afferent innervation is provided by ganglion cells of the spiral ganglion in the cochlea, which have central axons that form the auditory nerve. There are two types of afferent neurons: (1) type I neurons, which receive synapses from inner hair cells, and (2) type II neurons, which receive synapses from outer hair cells. The central axons of these ganglion cells form the auditory nerve. Efferent innervation is provided by a subgroup of neurons in the superior olivary complex that send axons to the cochlea and are hence called the olivocochlear (OC) neurons. There are two types of OC neurons: (1) lateral OC neurons, which innervate type I dendrites near inner hair cells, and (2) medial OC neurons, which innervate outer hair cells. Lateral OC neurons are distributed mainly ipsilateral to the innervated cochlea, whereas medial OC neurons are distributed bilaterally to the innervated cochlea, with approximately two-thirds from the contralateral (not illustrated) and one-third from the ipsilateral side of the brain. Bottom panel depicts auditory nerve fiber tuning curves, with a fiber tuned to 2000 Hz (left curve) and 15 000 Hz (right curve); frequency is shown on the x-axis. The y-axis is threshold in decibels sound pressure level. *Sources*: *Top*: Brown, 2003; *bottom*: Javel, 2003.

wave at the cochlea, to neural coding at the auditory nerve. A schematic of the pathways at the auditory brainstem is shown in Figure 7.7, top panel, with fibers that show a 'best' or center frequency response in the bottom panel.

Thus, in this manner, sounds travel from the external ear canal, through the middle and inner ears, and on to the auditory brainstem. At this stage, the information in sounds is transduced through fibers on its way to auditory cortex. You may have noticed that long before the information in sound reaches cortex, there are many recodings and transforms that occur. These transformations of sound inputs are key to understanding how the brain decodes the multiple complexities of an everyday listening environment, such as the college classroom example described early in this chapter.

2.0 THE CENTRAL AUDITORY SYSTEM

The information in sound undergoes many transformations as it ascends to auditory cortex. In this section, we will review the major aspects of the anatomy and neurophysiology of the central auditory system. The auditory system is comprised of many stages and pathways that range from the ear, to the brainstem, to subcortical nuclei, and to cortex. The three main divisions of the auditory system are the peripheral system, which we have already discussed, the pathways (ascending to cortex, descending from cortex, and parallel pathways across cortical sites), and the central (cortical) system. While each stage and pathway has functional significance in the decoding of sounds, it is important to consider the auditory system as a whole

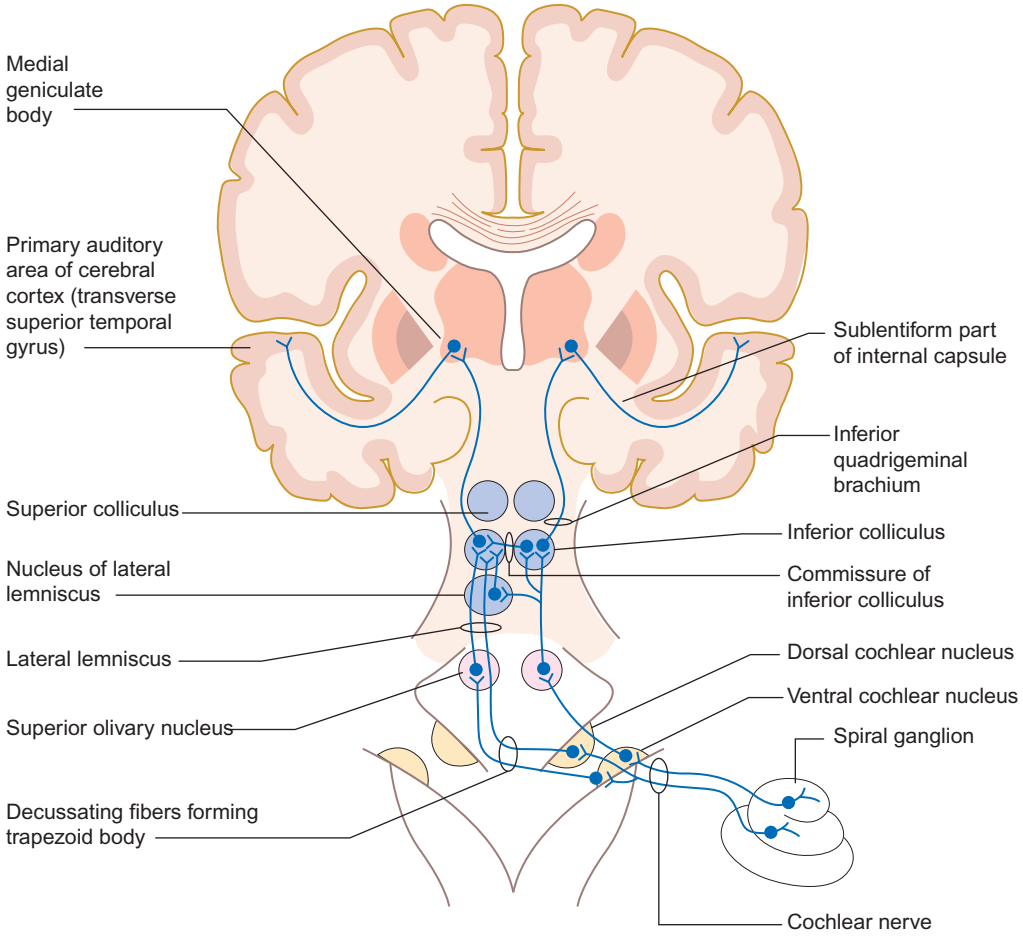


FIGURE 7.8 Illustration of the human auditory system showing pathways and subcortical nuclei in the ascending and descending pathways. *Source*: Standring, 2005.

because of the complex interactions across and within its constituent parts.

2.1 Auditory pathways

As we mentioned earlier, all sound processing occurs over time. The hallmark of the auditory system is its exquisite temporal resolution for decoding intricate information in sounds (Gage and Roberts, 2000; Gage *et al.*, 2006). One important aspect of the high temporal resolution of the auditory system is the fast and accurate transmission of sound information along and throughout its many pathways. Not only do transient features in complex sounds – such as the harmonic structure of consonants in speech or musical phrases – need to be conveyed rapidly from eardrum to cortex, but the information from the two ears needs to combined and integrated in a meaningful way en route. Let's discuss how and where this happens in sound processing.

The *ascending* (afferent) pathways transmit information about sounds from the periphery to cortex. There are many stages of computation along the way: this pathway is not a simple delivery system but entails a significant amount of encoding and recoding of information in the sounds. The neural signal travels from the auditory nerve to the lower (ventral) *cochlear nucleus*. The cochlear nucleus is tonotopically organized. From the cochlear nucleus, the signal continues along the ascending pathway through the lateral lemniscus, inferior colliculus, thalamus, to auditory cortex (Figure 7.8). This is not a single pathway, but is complex and includes many computational stages as well as the combination of sound inputs from the two ears. A key function of the ascending pathway is to evaluate the information from the two ears in order to localize sounds in space – and we will discuss this in more depth later in the chapter.

The *descending* (efferent) pathways from regions in the cortical and subcortical auditory system cortex to

the periphery are under direct or indirect cortical control. Recent research indicates that this control extends all the way to the hair cells in the cochlea! One important function of the descending pathway is to provide 'top down' information that aids in selective attention processes and in perceiving sounds in a noisy environment. The precise way in which the descending pathways function in sound processing is not well understood in humans. However, here is an example of some aspects of listening in which the descending pathways play a role. Imagine that you are having a very important conversation with a close friend as you stand outside a college classroom. You are focusing on the conversation, but meanwhile a motorcycle starts up in an adjacent parking lot, a helicopter passes overhead, and a gardener mows the nearby lawn with a power mower. You struggle to hear your friend, but manage to tune out most of these competing sounds. Suddenly the doors of the classroom open and scores of students erupt from the classroom, chatting and laughing. This may put an end to your conversation for a few moments, however, throughout the process of listening to your friend's voice during this noisy scene, your auditory pathways have been at work helping you both to focus your attention specifically to your friend and in extracting your friend's voice out of the competing noises coming at you from all directions.

The auditory pathways are not just ascending to or descending from cortex, there are many important connections between the auditory cortices in the left and right hemispheres via the corpus callosum. These connections between the hemispheres are tonotopically organized. There are also cortico-cortical pathways that provide integration of auditory processes with other sensory systems, as well as with working and long-term memory processes, and stored memories and knowledge. Together with the ascending and descending pathways, the cortical pathways represent complex connectivity patterns that are critical, not only for processing sound, but also for integrating information to other regions in the brain.

2.2 Auditory cortex

At last we have arrived at auditory cortex and, in this section, we will discuss the anatomy of brain areas in auditory cortex as well as the neurophysiological features of these regions of cortex. Auditory cortex is the region within cortex specialized for sound processing. It is located in each hemisphere within the Sylvian fissure on the surface of the supratemporal plane and the upper banks of the superior temporal gyrus (Figure 7.9).

As we have discussed, information in sounds is transmitted from the ear to auditory cortex via the ascending auditory pathways. Along the way, the signal is transformed and recomputed in many ways. Auditory cortex is not the end stage of this pathway, but serves as a hub or nexus for sound processing, interacting dynamically with other systems within cortex, across the hemispheres, and back down the descending pathways to the cochlea. These dynamic processes provide a wide range of perceptual acuity and allow us to perform complex perceptual tasks such as selectively listen to one person's voice in a crowded and noisy room or recognize a melody even though it is played in another key or at a different tempo. These perceptual tasks are so complex that we do not totally understand how the auditory system performs them. However, we do them every day with little or no conscious effort on our part.

Auditory cortex is not a unitary brain area but is comprised of several structural (anatomical) areas that differ in their role in decoding sound. Early descriptions of these areas within auditory cortex were made based on the structure, such as a gyrus within this cortical region, and by underlying neurophysiological features, such as the cytoarchitectonic classification. Although we do not fully understand the role of each area within human auditory cortex, work is in progress to map out regions within auditory cortex and their corresponding role in perception. We discuss our current knowledge about human auditory cortex below, with a description of the structure or anatomy followed by details regarding the cellular organization and response properties, or neurophysiology.

2.2.1 Auditory cortical anatomy

Much of what we know about auditory cortical anatomy comes from work in non-human primates (Galaburda and Pandya, 1983). In macaque monkeys, the major regions of auditory cortex are the core, belt, and parabelt regions (Figure 7.10, left panel). These distinct regions are distinguished by their cytoarchitectural, physiological, and connective properties. The core receives inputs from the thalamus and in turn projects to regions in the lateral belt areas (Kaas *et al.*, 1999). This anatomical and connective structure has led scientists to suggest that there is a hierarchical organization in auditory cortex, with subcortical projections to the core or primary auditory (A1) region. A1 is thought to decode basic properties or features in sounds. From A1, there are projections to the belt regions where more complex feature extraction processes occur (Kaas *et al.*, 1999).

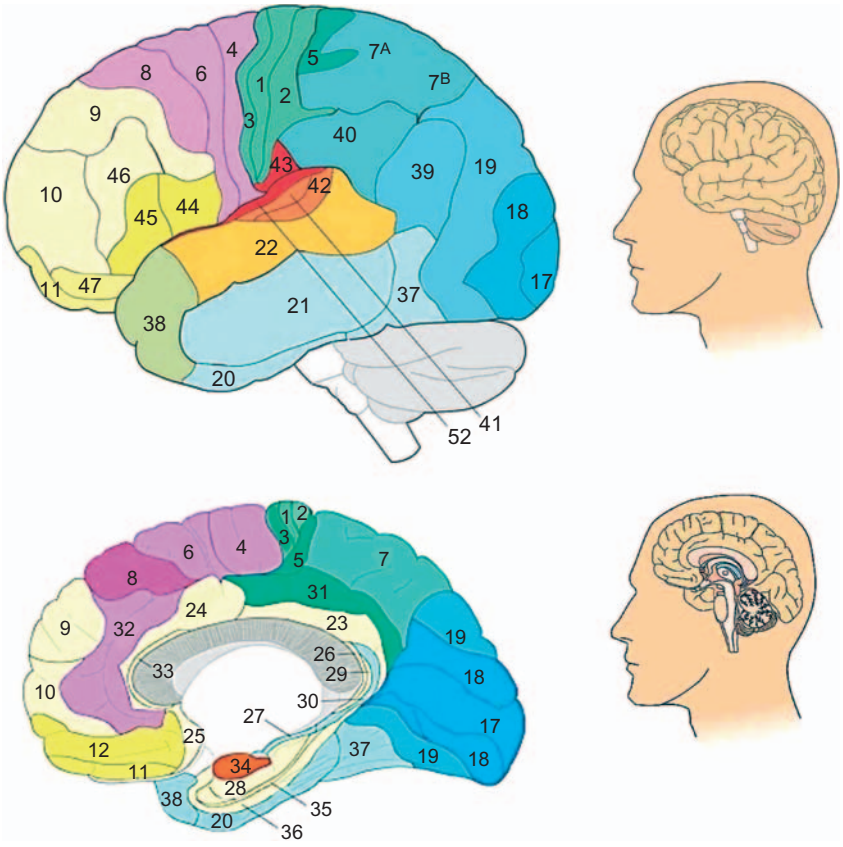


FIGURE 7.9 Top panel shows an illustration of the human brain from a lateral view, bottom panel from a medial view. Colored brain regions are adapted from Brodmann (1909). Auditory and receptive language cortical regions include Brodmann 22, 41, 42, and 52.

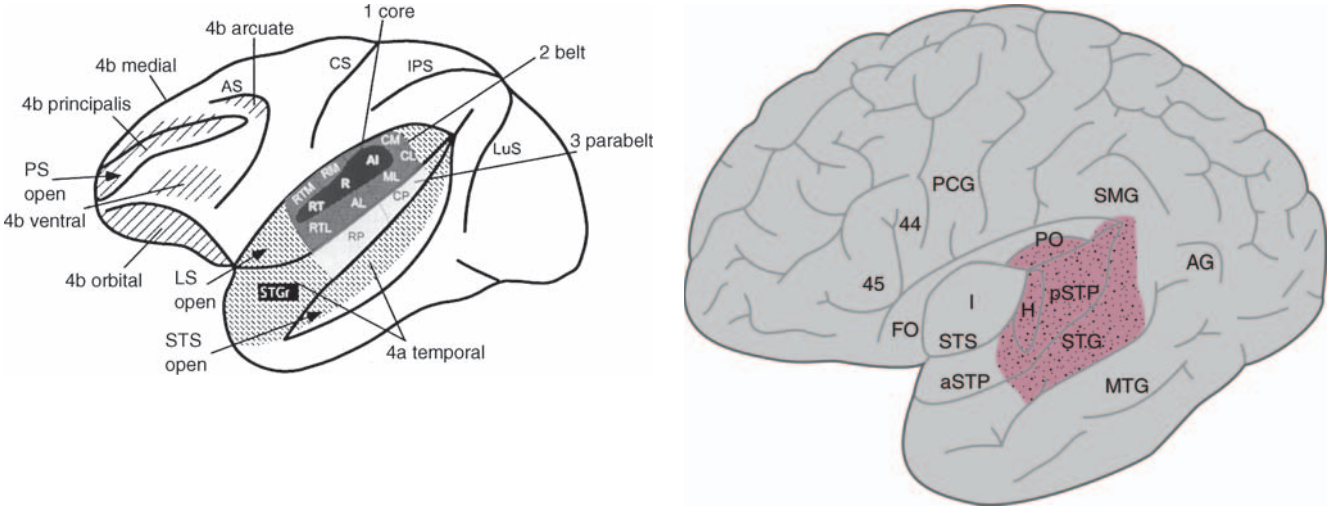


FIGURE 7.10 Left panel depicts levels and regions of auditory cortical processing in the macaque monkey. The areas shown are located on the superior temporal gyrus and in the depths of the superior temporal sulcus, which has been opened to show the extension of auditory-related cortex into this sulcus. Right panel depicts similar regions in the human, with the Sylvian fissure opened to show regions of auditory cortex on the supratemporal plane. (Adapted with permission from Zatorre, 2002.) *Source*: Caplan and Gould, 2003.

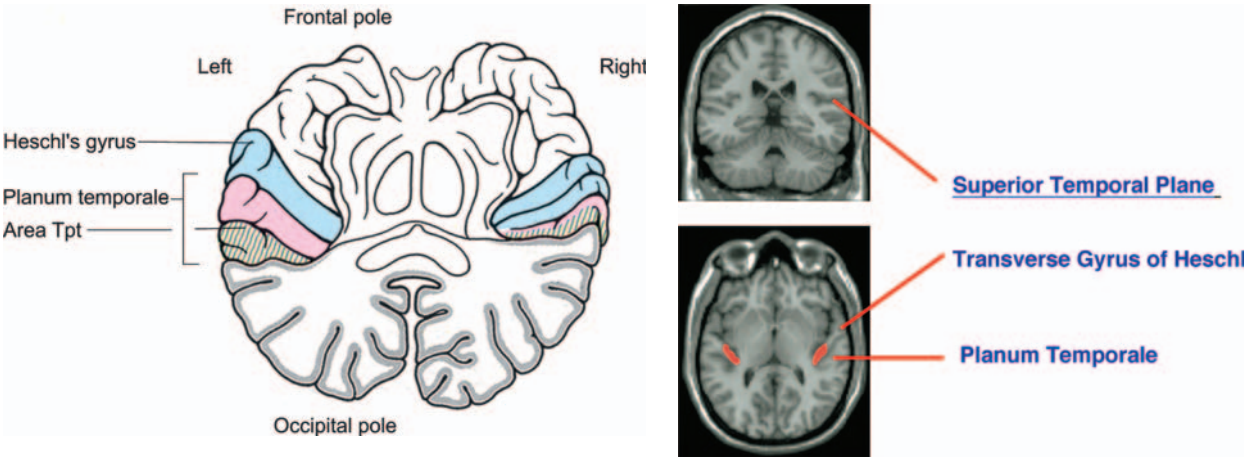


FIGURE 7.11 Left panel illustrates regions within auditory cortex, showing typical pattern of asymmetries in the left and right hemispheres. Right panel shows an MRI depiction of localizations of sound processing in the same regions. *Sources: Left*: Standring, 2003; *right*: Frackowiak, 2004.

The belt and parabelt regions surrounding A1 are specialized for sound processing and thus are unimodal auditory cortex. Human auditory cortex (see Figure 7.10, right panel) shows similar regions, with the Sylvian fissure opened to show regions of auditory cortex that correspond to the regions presented for the macaque in Figure 7.10's left panel.

In humans, primary auditory cortex is located within *Heschl's gyrus* (Figure 7.11, left panel) and is roughly analogous to core regions described in non-human primates. Heschl's gyrus corresponds to Brodmann's area 41 (Brodmann, 1909). Typically, primary auditory cortex comprises only a portion (one- to two-thirds) of the medial aspect of Heschl's gyrus. There is significant variability in the anatomy of Heschl's gyrus both in the two hemispheres and across individuals: Heschl's gyrus is typically located somewhat anterior (~6 mm) in the right hemisphere than in the left, and some individuals have more than one Heschl's gyrus. This structural variability in Heschl's gyrus has important implications when interpreting functional neuroimaging findings, since the actual size and location of Heschl's gyrus vary so much across individuals (Figure 7.11, right panel; Frakowiak, 2004).

Auditory cortex extends from Heschl's gyrus in the anterior-inferior direction and the posterior-superior direction along the supratemporal plane and the upper bank of the superior temporal gyrus. A second important anatomical region in human auditory cortex is the *planum temporale*, located just posterior to Heschl's gyrus. There are both hemispheric and individual differences in the planum temporale. However, unlike Heschl's gyrus, the differences fall into a general pattern: the *planum temporale* is typically much larger in the left hemisphere than in the right. In fact, the left planum temporale can be up to ten times larger in the left hemisphere in right-handed individuals (Figure 7.11, left panel). Planum temporale asymmetries were reported in a series of anatomical studies by Geschwind and colleagues (Geschwind and Galaburda, 1985a, b, c). These scientists noted that language function tends to be lateralized to the left hemisphere. They suggested that the larger left hemisphere planum temporale reflects its role in decoding auditory language. More recent neuroimaging studies, however, have provided a method to specifically test this hypothesis and provide differing views of the role of the planum temporale in sound processing. Just anterior to Heschl's gyrus is the planum polare. This region has not been the focus of much study in humans, and little is known about its role in auditory perception. Posterior to the planum temporale and unimodal auditory areas is Brodmann area 22. This is the area that Carl Wernicke hypothesized played an important role in speech comprehension (Wernicke, 1874/1977). According to Wernicke, this region was not an auditory region per se, but formed the language area for speech comprehension processes that were closely related (physically and functionally) to auditory processes. This region is typically referred to as Wernicke's area.

2.2.2 *Neurophysiology*

Several guiding principles of auditory cortical organization have been established in studies of cats and

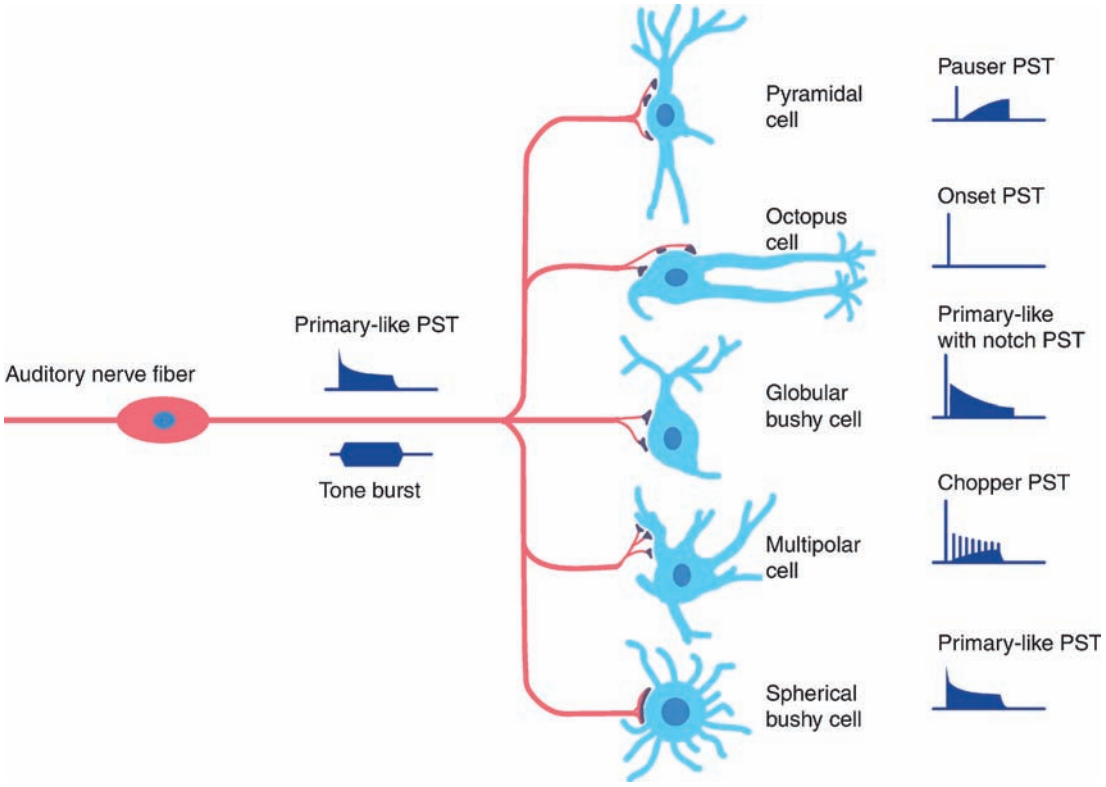


FIGURE 7.12 Schematic of the main anatomical cell types of the cochlear nucleus and their corresponding post-stimulus time (PST) histograms. *Left*: An auditory nerve fiber is shown with its typical response, a primary-like PST. *Center*: The auditory nerve fiber divides to innervate the main cochlear nucleus cell types. *Right*: PST histograms corresponding to these cell types are shown. In their PST histograms, pauser units fire an initial spike and then have a distinct pause before a slow resumption of activity. Onset units fire mainly at the tone burst onsets. Primary-like units get their name from the similarity of their PSTs to those of primary auditory nerve fibers, but the primary-like with notch type additionally has a brief notch following the initial spike. Chopper units have regular interspike intervals that result in regular peaks in the PST. Most of these patterns are very different from the primary-like PST and irregular interspike intervals of the auditory nerve fiber. For histograms, the sound stimulus is typically a 25 ms tone burst with frequency at the center frequency of the neuron and sound level at 30 dB above threshold. *Source*: Brown, 2003.

non-human primates. The basic units of organization in auditory cortex, as in other cortical sensory areas, are neurons, cortical columns, and neural networks. There are several differing types of neurons in the auditory system (Figure 7.12). These neurons have different response properties for coding frequency, intensity, and timing information in sounds as well as for encoding spatial information in processes for localizing sounds in space. Most cortical neurons respond to binaural inputs (inputs from both ears), demonstrating the importance of cortical processes for decoding binaural information for sound localization and other complex hearing processes. Together, these differing types of neurons form a dynamic network that encodes transient features in sounds. Far less is known about the types of neurons in human auditory cortex. However, the large pyramidal cells that are distributed along the supratemporal plane likely play a key role in sound processing.

Mapping receptive field properties of neurons in auditory cortex has been the focus of many animal studies. A large proportion of auditory cortical neurons have inputs from both ears. However, the two ears are not represented in the same way within each hemisphere. In auditory cortex in the left hemisphere, the right ear, the *contralateral* ear, has a much larger or stronger representation than the left ear, the *ipsilateral* ear. A similar and opposite pattern is observed in the right auditory cortex, with a stronger representation of the left ear versus the right. This general asymmetry for the representation of the two ears in binaural hearing holds true for humans as well (Woldorff *et al.*, 1999).

One important aspect of decoding features in sounds is determining where the sound is in relation

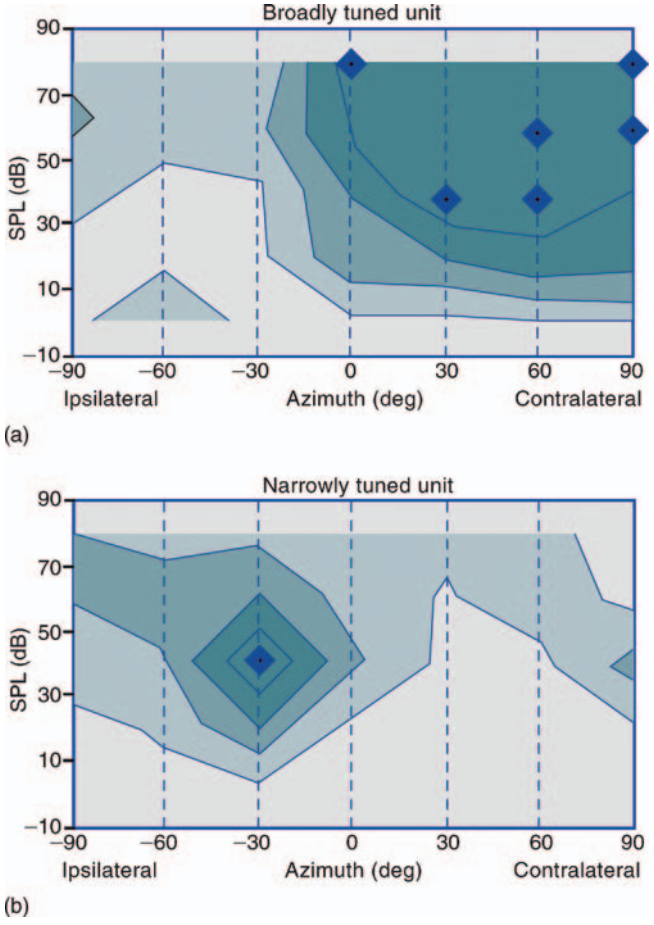


FIGURE 7.13 Receptive fields of two auditory cortex neurons plotted as a function of sound pressure level and azimuth in the frontal hemifield. Noise bursts were used as stimuli. Small diamonds show points of maximal response, and progressively lighter shading shows regions of progressively smaller response. Zero degrees azimuth refers to directly ahead, and positive azimuths refer to points in the contralateral hemifield. *Source*: Brown, 2003.

to the listener. In Figure 7.13, we show receptive field properties of two auditory cortical neurons as a function of where the sound is located in space relative to the head (the x-axis), and of how loud the sound is (the y-axis). The receptive field of the neuron presented in the top panel shows a large shaded region across sounds coming from the contralateral ear and across a lot of sound intensities. These receptive field properties indicate that this neuron is *broadly tuned* to sound information across loudness levels from the contralateral ear. In the lower panel, the neuron shows a sensitivity that is much more narrowly focused, in this case to sounds that are presented at 30–60 dB and coming from the ipsilateral ear. This neuron is *narrowly tuned*. Broadly and narrowly tuned neurons play differing roles in sound processing. A broadly tuned neuron may not provide detailed information regarding just where a sound is located in space or precisely how loud it is. However, this neuron will be highly sensitive to detecting any sound within a large loudness scale coming from the contralateral ear. Thus, this neuron may be important for the *detection* of the presence of a new sound and provides general information about which ear the sound is coming from. A narrowly tuned neuron will provide more specific information regarding where a sound is, not just which ear but where in space on that side of the head, as well as more specific information about how loud the sound is. Thus, this neuron may be important for the *discrimination* of finer details about a sound.

As in other cortical sensory regions, auditory cortex has a *columnar organization*, meaning that neurons are organized into columns that span across all six cortical layers (see Chapter 3). Within an individual column, neurons show similar response properties. A general scheme for the columnar organization in auditory cortex is that neurons that respond to binaural inputs are organized into alternating columns that have differing roles in sound processing, either causing an excitatory (summation) or inhibitory (suppression) effect on information coming from the two ears (Brugge and Merzenich, 1973). These complex interactions of summing or suppressing the information coming from the two ears likely underlie perceptual functions, such as selectively attending to information coming from one ear.

A central guiding principle for non-human auditory cortex is the *tonotopic* organization. Within the core in cat auditory cortex, for example, receptive fields of neurons reflect a tonotopic organization in primary (A1) regions that has a mirror image in adjacent (anterior and posterior) core regions (Figure 7.14).

While the basic aspects of neurophysiology are likely similar for humans, the uniqueness of human speech, language, and music perception, as well as the substantially larger regions of cortex devoted to auditory cortex in humans, probably mean that there are neurons and networks that are specialized for these complex processes and specific to human auditory cortex. For example, although many auditory cortical regions in non-human primates reflect a tonotopic organization, evidence for tonotopy has been less robust in human studies and may be limited to primary auditory cortex and not represent the basic organizational principle in non-primary auditory areas (Wessinger *et al*., 2001). The investigation of the organizational principles of human auditory cortex is a work in progress, much aided by the advent of new

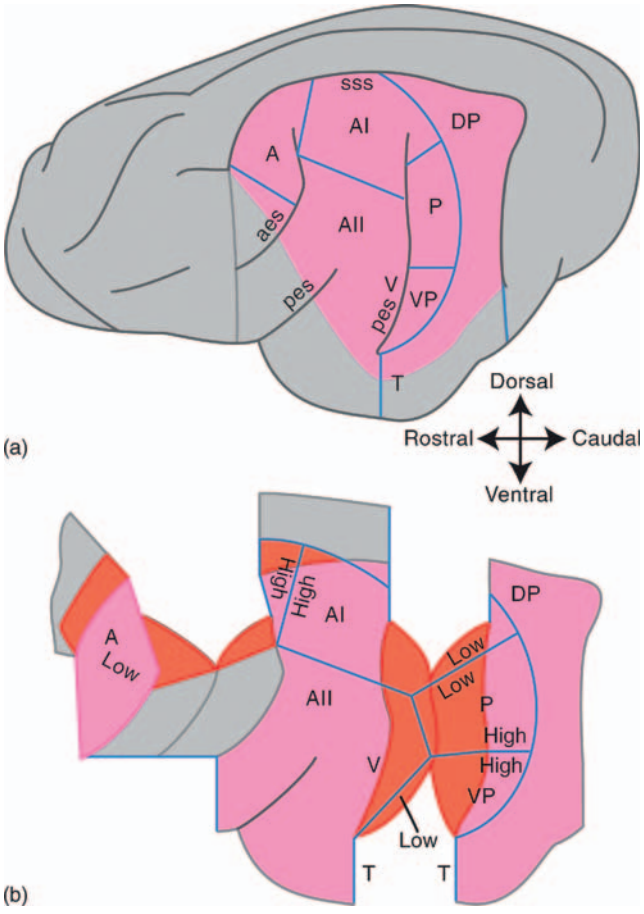


FIGURE 7.14 Auditory cortical fields in the temporal cortex of the cat. (a) Lateral view. (b) Lateral view that is 'unfolded' to show the part of the fields that are normally hidden within the sulci (orange shading), as well as the high- and low-frequency limits of the tonotopic fields. The four tonotopic fields are the anterior (A), primary (AI), posterior (P), and ventroposterior (VP). Positions of the lowest and highest center frequencies in these fields are indicated in (b). Note that at the boundaries of the tonotopic fields, the direction of tonotopy is reversed so that adjacent fields have 'mirror-image' tonotopy. Other cortical fields have less rigidly organized tonotopy or little tonotopy. These fields are secondary (AII), ventral (V), temporal (T), and dorsoposterior (DP). Also indicated are suprasylvian sulcus (sss) and anterior and posterior ectosylvian (aes, pes). *Source*: Brown, 2003.

techniques for its study, such as transcranial magnetic stimulation (TMS) and fMRI.

3.0 FUNCTIONAL MAPPING OF AUDITORY PROCESSING

Within auditory cortex, are there sub-regions that are specialized for decoding different types of sounds such as tones versus speech versus music? Or are all areas of auditory cortex involved in all sound processing, regardless of the class of stimulus? Are sounds processed identically in the left and right hemispheres or are there subtle differences? Auditory scientists are still unraveling these puzzles. The advent of neuroimaging techniques has provided us with new ways to investigate brain areas for sound processing. Much of this work has been motivated by the investigation of brain regions that may be specialized for decoding speech and language. While neuropsychological studies of patients with brain damage have provided a wealth of information regarding specific language deficits and their correspondence to brain areas, neuroimaging allows the investigation of speech and language processes in healthy individuals. Neuroimaging also provides a way to investigate aspects of auditory function that have not been able to be addressed before, such as what brain areas are involved in imagining a sound versus hearing a sound? And what happens in auditory cortex while we sleep?

3.1 Primary auditory cortex

We have discussed a hierarchical model for sound processing, developed in animal studies, with neurons in primary auditory cortex tuned to extract basic physical features in sounds while neurons in non-primary auditory cortex are tuned for extracting more complex features. Recent studies in humans have provided evidence that this hierarchy is present in human auditory function, with basic features in sounds encoded in primary auditory cortex and more complex information in sounds encoded in the planum temporale (Wessinger *et al*., 2001). This area of investigation is still in its early stages, and so we must treat these initial findings with a bit of caution until we have learned more. Thus, the investigation of the functional role of human primary auditory cortex is still unfolding, and it is likely that human auditory areas serve somewhat differing functions from those found for non-human species.

3.2 The role of the planum temporale in sound decoding

Early anatomical studies provided evidence for an important asymmetry in human auditory cortex: the planum temporale (PT) was much larger in the left hemisphere for right-handed individuals (Geschwind and Levitsky, 1968). The prevalence of this asymmetry and its location in auditory areas close to Wernicke's area for speech comprehension motivated the hypothesis that PT was the site for auditory speech and language

processing. This idea has been supported by neuroimaging studies investigating the functional role of PT in speech perception. However, neuroimaging studies of PT response to different classes of speech and non-speech sounds provide evidence that the functional role of PT is not limited to speech sounds. These findings have resulted in a new assessment of the role of PT in sound processing. New light has been shed on the role of PT in sound and language processing by Hickok and his colleagues. In a recent review of the functional neuroanatomy of language, Hickok points out that it is perhaps not surprising that the PT seems to respond to so many classes of sounds and for such a wide variety of tasks. If you look at the PT in terms of its cellular (cytoarchitectonic) structure and organization, then you will see that within the anatomical bounds of this region lie four distinctly different fields (Figure 7.15). These differing fields likely correspond to differing functions performed within this area and may explain why PT is activated in so many neuroimaging studies for a wide variety of tasks and stimulus types. Much more investigative work is needed in order to provide a thorough account of the role of functional areas in human auditory cortex, such as the planum temporale.

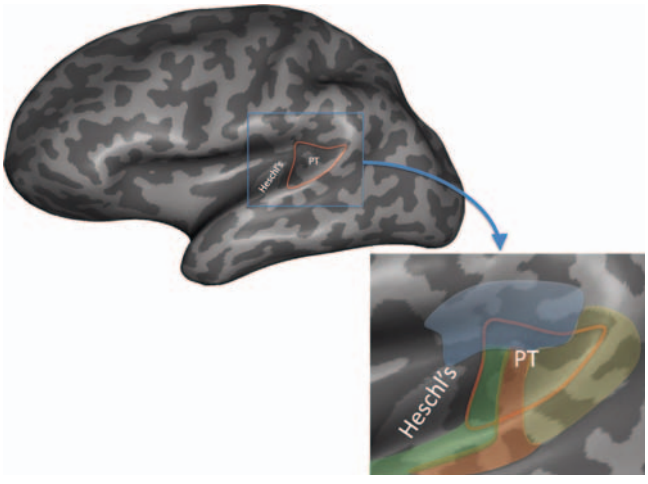


FIGURE 7.15 Just what role does the PT play in sound and language perception? Cognitive neuroscientists are still assessing the PT's role in auditory processing. A recent review of the functional neuroanatomy of language by Hickok (2009) shows that the area we refer to as PT is likely not a unitary functional region at all. If you look at the PT in terms of its cellular (cytoarchitectonic) structure and organization, then you will see that within the anatomical bounds of this region lie four distinctly different fields (shown in green, red, yellow, and blue). These differing fields likely correspond to differing functions performed within this area and may explain why PT is activated in so many neuroimaging studies for a wide variety of tasks and stimulus types. *Source*: Hickok, 2009.

3.3 Cortical auditory 'what' and 'where' systems

The central role of the auditory perception system is to extract information from the listening environment in order to determine what is happening around us. Consider again the large college classroom where doors are opening and closing, students are talking, backpacks are being unzipped, books are being dropped on desktops. All of these sound events are happening at the same time and are overlapping in frequency and intensity. How does the auditory system decode the individual auditory 'objects' such as a friend's voice, a door shutting, a cell phone ringing? To accomplish this, the auditory system must keep track of many aspects of the complex auditory scene: *where* sounds are occurring in space, *when* sounds occur – are they simultaneous or does one sound precede another? – to determine *what* the sound represents in terms of known auditory objects such as speech or music or new auditory objects to be learned. Of course, these perceptual tasks are not limited to the auditory system but make contact with other sensory systems as your brain integrates what you hear with what you see, feel, and smell. These tasks also interact with your memories and learned information already stored regarding auditory objects that have taken a lifetime to develop. Let's begin with some auditory perceptual processes within the framework of the auditory system.

3.3.1 'Where' system: sound localization

An important aspect of auditory scene segmentation is to know where a sound is coming from. Imagine a busy airport baggage area where you are waiting for a friend to arrive. The area is full of people talking. There are frequent public address announcements: this is a complex auditory scene! Eventually your friend spies you and calls out: 'I'm over here!' This is not extremely helpful to you because you don't know where 'over here' actually is, calling out, 'I am 10 feet (3 m) behind you and slightly to the right!', would seem to be somewhat more useful (although it actually is not: sound localization computations are much faster than speech comprehension). Despite the limited information in 'over here', you will likely spin around and make visual contact quickly. This is your auditory system doing what it does best: localizing sound even in complex listening environments with many competing sounds.

Sound localization is a fundamental process for the auditory system. Knowing where a particular sound is

coming from is quite useful in decoding the auditory scene, but of course, it is also critical for survival – allowing us to jump out of the way of an oncoming car or to duck when we hear a loud noise. How does the brain locate sounds in space? You may have an intuition that this is a much more difficult process in some ways than the way the visual system maps the visual scene in space (see Chapter 6). Sounds are always changing in time and the mapping of auditory space is a complex one. Here is how it works: when a sound occurs, it will likely be off to one side or the other of you. It could also be behind you. In order to determine where the sound is in relation to you, your auditory system must make a very quick determination of the sound's arrival at the two ears. Two basic types of cues are used when our system localizes sound. The first is the *interaural (between ear) time difference*: the difference in time between a sound reaching your left ear versus your right. A second important cue for localizing sounds is the *interaural level difference*. This is the small difference in loudness that occurs when a sound travels toward the head from an angle. The head produces a 'sound shadow', so that sounds reaching the far ear are somewhat quieter than the near ear and the absolute level differences depend on the frequency of the sound. (See Figure 7.16.)

Thus, sound localization processes rely on the basic notion that if a sound occurs to the left of you, it will make contact with the eardrum of the left ear slightly before the right ear and it will be slightly louder in the left ear than in the right. The actual computations that produce sound localization functions involve complex algorithms called *head-related transfer functions* to calculate the location of sounds in auditory space. The neural computations that underlie sound localization are not well understood. One central 'problem' that these computations must address is the fact that the human head changes size rather dramatically throughout childhood. The neural code for the head-related transfer functions must be able to take into account a changing head size.

Recent investigations show that these computations are performed both in subcortical and cortical auditory regions. However, there remains some debate as to how these regions interact. For example, in a series of MEG studies to evaluate the cortical dynamics of spatial processing, Tiitinen and colleagues (Tiitinen *et al*., 2006) have reported that while both left and right auditory areas appear to be involved in decoding spatial information, the right hemisphere response is more prominent (Figure 7.17). Does this mean that the right hemisphere is specialized for decoding sound localization information? Probably not: while there may be a subtle bias in the right hemisphere for processing spatial information, more studies are required in order to map out how complex and time-varying spatial information is decoded in auditory cortex.

There is, however, general agreement that the interaural time and level differences for sound localization are minuscule (fractions of a millisecond) and demand

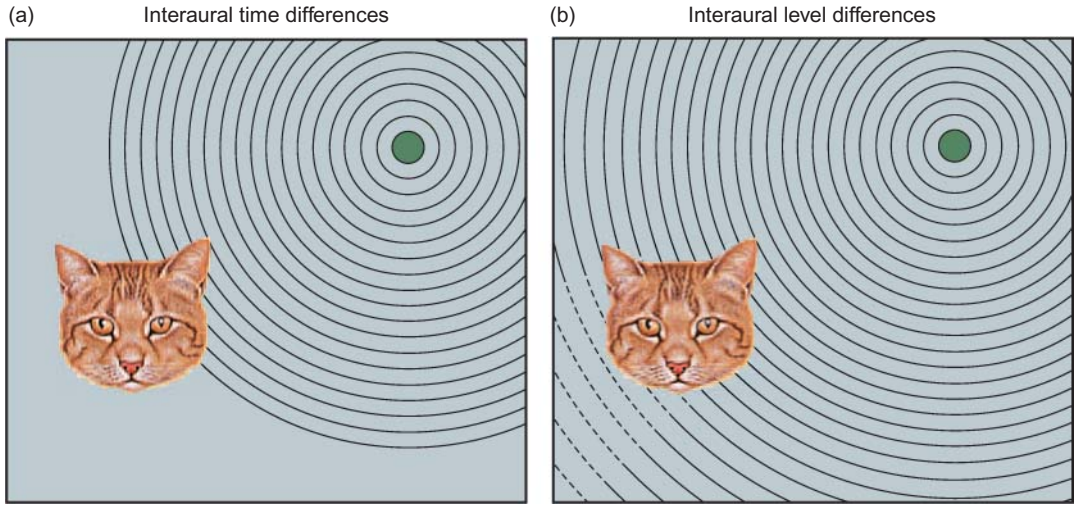


FIGURE 7.16 We present a schematic drawing to illustrate the two cues for binaural sound localization. The sound source is shown as a solid dot to the right of the cat's head. The sound waves produced by the sound are shown as concentric lines. (A) *Interaural time differences* result because it takes the sound waves longer to travel to the ear away from the sound source. (B) *Interaural level differences* result because the head forms a 'sound shadow,' which reduces the level (loudness) of the sound at the ear more distant from the source. *Source:* Brown and Santos-Sacchi in Squire et al., 2008.

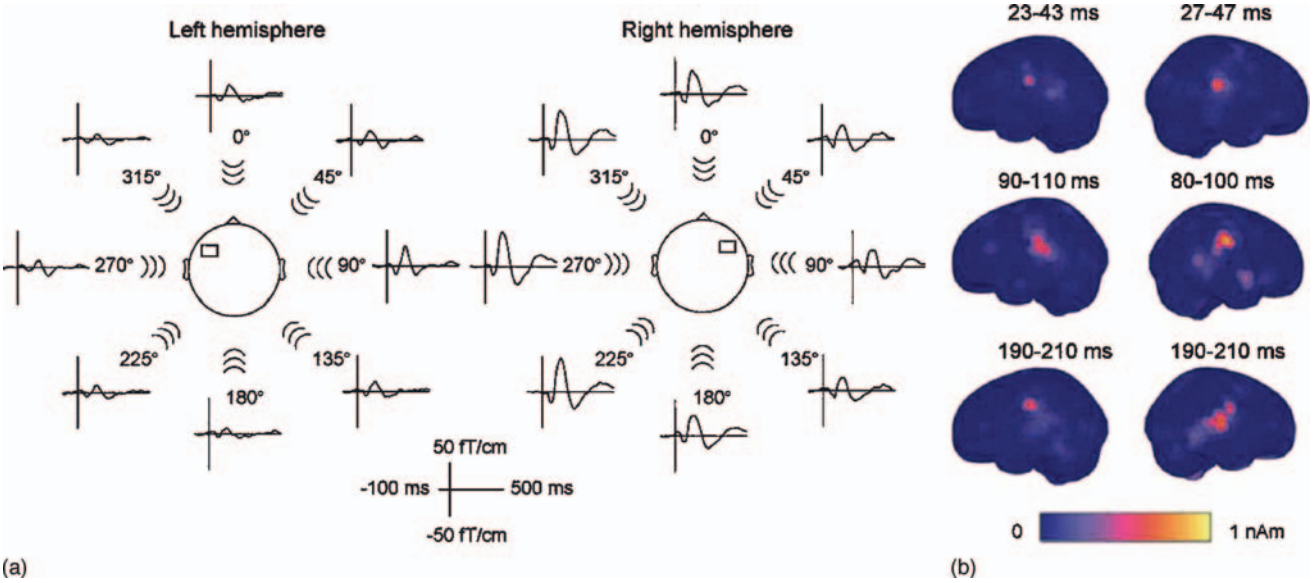


FIGURE 7.17 The P1 m, N1 m, and P2 m responses as indicators of the cortical processing of sound source direction. Realistic spatial sound was presented from eight equally spaced source directions in the azimuth plane. (a) Grand-averaged MEG responses. Sounds from each source direction elicited a response complex comprising the P1 m, N1 m, and P2 m. The right-hemisphere P1 m and N1 m peaked earlier for sound sources contralateral to the hemisphere. The amplitude of the P1 m and N1 m in both hemispheres and the right-hemispheric P2 m varied according to the sound source direction. Overall, sound sources in the contralateral hemisphere resulted in larger peak amplitudes, and the right-hemispheric responses were larger in amplitude than the left-hemispheric ones. (b) Grand-averaged minimum current estimates (MCE) obtained at the latencies of the P1 m, N1 m, and P2 m to the 3D sound from the direction angle of 90 degrees. Activation restricted to the vicinity of the auditory cortex was observed at each latency. *Source*: Adapted with permission from Tiitinen *et al.*, 2006.

a system that can decode tiny differences in sounds with amazing precision. In fact, the encoding systems for localizing sound form the basis of complex hearing and likely form the neural underpinnings of speech and music perception in humans.

A 'where' system for spatial attention

While most auditory cortical neurons respond to inputs from both ears, the response is asymmetric, with a stronger representation of information from the contralateral ear compared to the ipsilateral ear. Is there a similar effect for attending to different sides of auditory space? Early investigations by Hillyard and colleagues provided evidence that there is. Using event-related potentials (ERPs), Hillyard reported a predominant N1 larger response for the attended ear in contralateral cortex (Hillyard *et al.*, 1973). More recent neuroimaging studies have also provided a way to investigate the effects of selectively attending to auditory space, confirming the earlier findings by Hillyard with different methodology (Tzourio *et al.*, 1997; Woldorff *et al.*, 1999). In a PET study, higher levels of activation in right auditory cortex were found when subjects attended to the left, and higher levels of activation in left auditory were found when subjects attended to the right (Figure 7.18) (Tzourio *et al.*, 1997).

This study is an example of 'top down' processing: rather than presenting sounds to the left or right side of the subject, the investigators merely instructed the subject to attend to the left or the right side of auditory space. These results demonstrate the powerful role of attention in the auditory system. And, since the hemisphere differences are due to the subject's attention being focused in differing auditory spatial locations, it also demonstrates the importance of careful experimental design when using neuroimaging techniques to investigate auditory cortical processing. For example, if you were investigating hemisphere differences for vocal music versus instrumental music, it would be important to make sure your subjects were not attending to just the left or just right side of auditory space while listening!

Expertise in spatial attention networks

While the role of attention in processing spatial information has been studied for many years, we are still unraveling some of the mysteries of how our brains

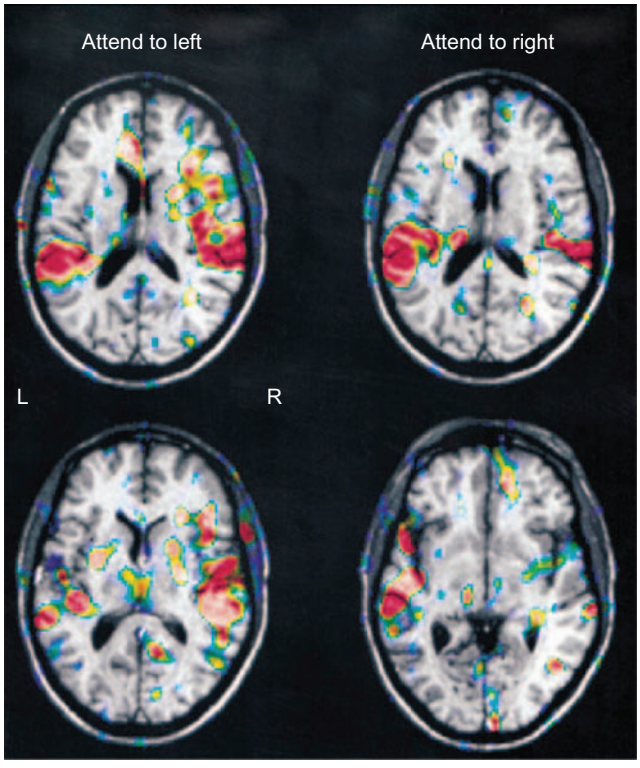


FIGURE 7.18 Example of individual PET activation images obtained at the Heschl's gyrus level (top) and through the superior temporal gyrus (bottom) in one subject. Left column, attend to the left deviant sounds versus rest; right column, attend to the right deviants versus rest. *Source*: Adapted from Tzourio *et al*., 1997.

accomplish the complexities involved in these processes. One focus of recent study is investigating individual differences in how individuals use attentional processes in decoding spatial cues. While this area of study is still in its early stages, we highlight a study by Munte and colleagues (Munte *et al*., 2001) where musical conductors' use of spatial attention was contrasted with other musical individuals (pianists) and a control group of non-musicians. The underlying notion was that a conductor must be able to attend to many spatial locations at once as he or she is leading a large number of musicians in playing a musical score. Munte and colleagues reported that conductors showed a higher sensitivity for sounds presented in peripheral listening regions than either of the other groups (Figure 7.19).

While these findings are intriguing, more studies must take place before we may understand the types of individual differences that occur in spatial attention processes.

3.3.2 'What' system: auditory object recognition and scene analysis

Our knowledge about sounds and what they mean begins before birth (see Chapter 15) and continues throughout life as we experience complex auditory scenes. You can imagine that the neural processes for decoding the college classroom example that we have used throughout this chapter did not get established overnight, but are the outcomes of years of experience. In this section, we will discuss the learning processes associated with forming mental representations of auditory objects as well as those for decoding complicated listening environments. Let's begin with auditory objects.

Auditory object recognition

Knowing *where* a sound is coming from is an important aspect of auditory scene analysis and critical for survival. The next step is to understand *what* you are hearing. To accomplish this, the auditory system must decode sounds 'online' as they occur in order to form a percept of a sound event or auditory object. These objects are learned over time as we grow from infant, to child, to adult, and they change with experience throughout our lifetime. Auditory objects can take many shapes, similar to visual objects, and vary widely in complexity from a simple computer alert chime, to the slamming of a car door, to a friend's voice, to a symphony. It seems that the brain has a nearly limitless capacity for storing and retrieving auditory objects. Auditory objects are organized into categories, such as human voices, musical instruments, animal sounds, that aid us in decoding learned objects as well as learning new ones. Over time, associations are formed between learned auditory objects and coinciding inputs from other sensory systems and these different sensory memories become integrated in the conceptual representation system. Early work on describing how these sensory inputs are experienced and combined to form conceptual knowledge was provided by Carl Wernicke, who proposed that with experience, when you hear the sound of a bell, you will recognize it as such and the sound of the bell will also bring to mind (activate) the visual features of a bell, the feel of a bell, etc. (Wernicke, 1874/1977).

Because language is uniquely human, it is probably not surprising that there have been many investigations into how the brain decodes speech. We will discuss these later in this chapter. For now, let's focus on how the brain decodes non-speech sounds such as environmental sounds. Here we highlight a recent

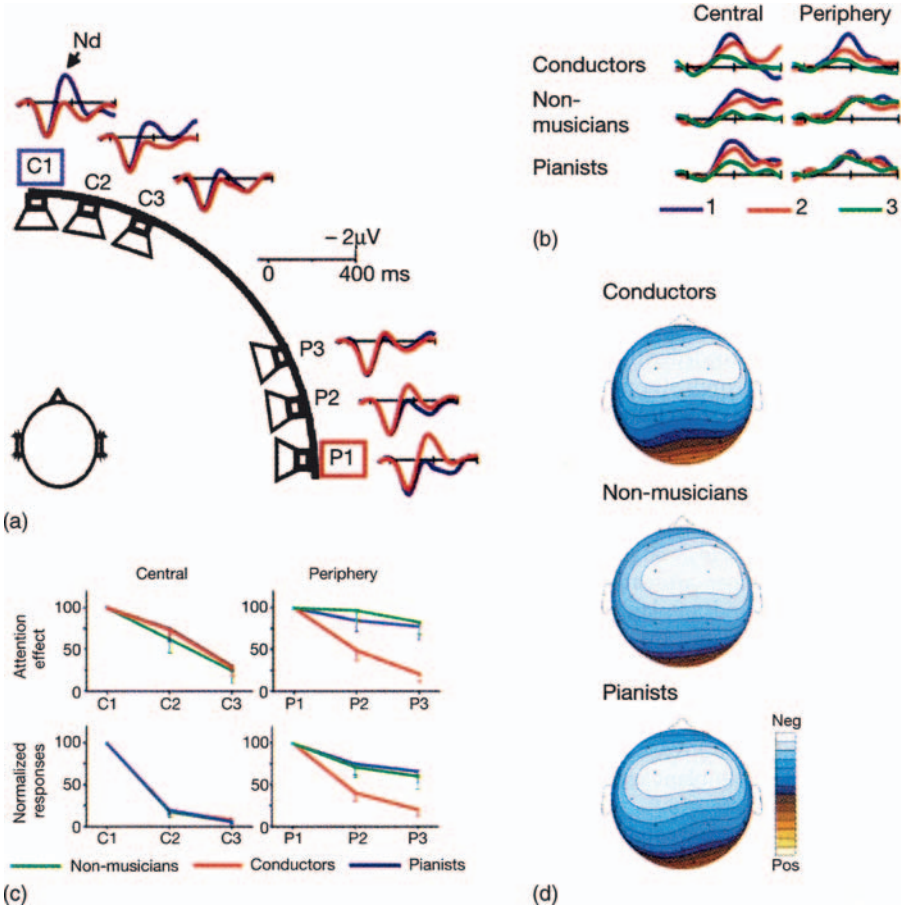


FIGURE 7.19 Effects of auditory attention in conductors, pianists, and controls. (a) Experimental setup; speakers are spaced 6 degrees apart. Group-average event-related potentials (ERPs; frontal midline site) recorded from the conductors and invoked by frequent standard stimuli are represented by blue lines that indicate response to stimuli from a particular speaker when attending to loudspeaker C1; red lines represent ERPs in response to the same stimuli when attending to speaker P1. Attended stimuli give rise to an enhanced negativity starting at 60 ms. ERPs associated with adjacent speakers show a similar declining gradient. (b) Difference waves obtained by subtracting unattended-direction from attended-direction responses. All subject groups showed a gradient ERP for central locations, for peripheral sounds, a gradient is evident only for the conductors. (c) *Top row*: Electrophysiological attention effect (frontal midline electrode, mean amplitude, 180–220 ms; C1/P1 set to 100%). No differences between groups were found for central locations. Conductors show steeper gradient in the periphery. *Bottom row*: Button presses in response to infrequent stimuli. For peripheral sounds, conductors show a decreased false alarm rate for adjacent locations. (d) Spine-interpolated scalp maps of the attention effect for the centermost speaker (time window, 180–220 ms) show a similar topography across groups. *Source*: Adapted from Munte *et al.*, 2001.

study by Binder and colleagues (Lewis *et al.*, 2004) who investigated brain areas for recognizing environmental sounds (e.g. the sounds of a doorbell, a hammer pounding a nail). Results are presented in Figure 7.20: the key finding was that auditory areas in the superior temporal gyrus were activated by both recognized and unrecognized (reversed) environmental sounds. However, recognized sounds also activated regions in the superior temporal sulcus and the middle temporal gyrus (MTG) in both hemispheres. These results are interesting in light of previous investigations of the functional processes of the MTG: the regions identified in this study partially overlap with semantic systems and with areas that have been reported as important for recognition of visual objects such as tools. During the process of learning an environmental sound, it is likely that the sound of a hammer will be heard at the same time movement of the hammer is seen. Thus, the sound and the sight of hammering are likely to be linked during the process of learning.

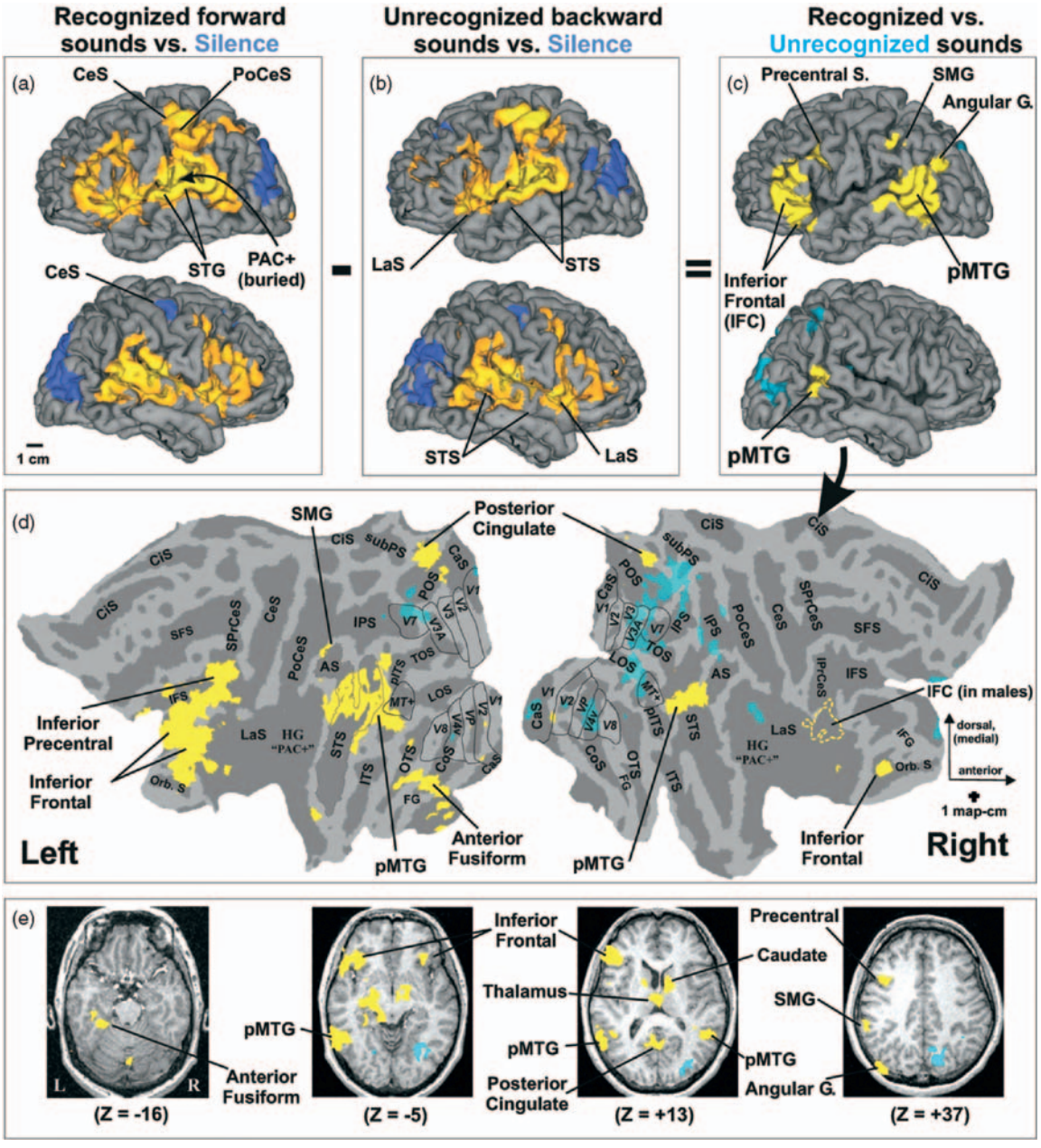


FIGURE 7.20 Brain regions involved in environmental sound recognition. Yellow hues show group-averaged activated regions and dark blue shows relative decreases evoked by (a) recognizable, forward sounds relative to silence or (b) the corresponding unrecognizable, backwards sounds relative to silence. (c) Data from (b) subtracted from (a), revealing regions preferentially involved in recognizing sounds (yellow) versus not recognizing the corresponding backward-played sounds (light blue), both relative to silence. (d) Flat maps showing data from (c). The left superior temporal sulcus is outlined in gray for clarity. (e) Axial sections of data from (c) displayed on the brain of one subject. *Source*: Lewis *et al.*, 2004.

Binder and colleagues propose that this is the case and that the MTG region is a likely candidate for the brain region for this type of object recognition processing.

The results of the study by Binder and colleagues (Lewis *et al.*, 2004) are in good accord with earlier studies of individuals with brain lesions who suffered from auditory agnosia, the inability to recognize auditory objects. Cases where the patient suffers from a specific ('pure') deficit for recognizing environmental sounds, while leaving speech recognition intact, are rare. The investigations of the cases that do exist have reported a complex location of lesions, with reports of left hemisphere damage, right hemisphere damage, or in some cases bilateral damage (see Clarke *et al.*, 2002). The results of Binder and colleagues, showing auditory object recognition – related activity in several

areas in both hemispheres, provides evidence that the neural substrates of auditory environmental object perception are likely complex and include multiple regions in both hemispheres. This work is an example of how the results of lesion studies inform scientists using neuroimaging techniques to investigate complex cortical processes.

The cocktail party effect

We have described how a sound is decoded by the auditory system to be recognized or learned as an auditory object. This process seems relatively straightforward when you consider a situation where a single sound event occurs in a quiet environment. But how is this perceptual task accomplished in noisy environments, with complex sounds that occur simultaneously in time, with overlapping frequencies, and possibly coming from the same spatial location? How does the auditory system distinguish them as separate sound events? This perceptual task – the 'cocktail party problem' (Cherry, 1953) – has been the subject of many investigations of auditory perception from a theoretical perspective to understand how the auditory system extracts information from complex signals as well as a practical perspective in designing speech recognition systems. Bregman (1990) provided a model to describe how the auditory system segregates the many different signals in a noisy environment. The four elements in this model are:

1. the source
2. the stream
3. grouping
4. stream segregation.

The *source* is the sound signal itself. The *stream* is the percept related to the sound. This distinction between the physical signal and the related perception is analogous to the relationship we described earlier in this chapter between the frequency (in Hz) of a sound and the pitch perceived by the listener: the source represents the physical features of the signal which can be well described in terms of its frequency, intensity, spatial location, etc., while the stream represents the psychological aspects which may vary widely across individuals.

Grouping refers to how the signals are perceptually combined to identify and maintain attention to some aspects of the auditory scene (such as listening to one friend's voice in a crowd of people). Perceptual grouping processes create the stream. There are two basic types of grouping: *simultaneous grouping*, where if two or more sounds have common onsets and offsets, they may be grouped together. Think of a choir or an orchestra: you will not typically hear each individual voice or instrument, but will group them into a single stream due to the beginning and ending of their music together as well as their shared spatial location. (On the other hand, if you pay particular attention, you can attend to a single voice or instrument: this is the dynamic auditory system at work!) *Sequential grouping* refers to the process in which features or properties are shared across sounds that occur over time. An example of this grouping process is if you are listening to a professor lecture and someone in front of you coughs. The stream coming from the professor is interrupted by the cough but you will likely not notice an effect in hearing what is being said. This is your auditory system recognizing that the professor's voice represents a single stream despite the brief interruption produced by the cough.

Stream segregation uses the grouping processes to segregate separate auditory objects or events into streams. Here are the basic grouping principles that Bregman developed in his model:

1. Proximity: sounds that occur close together in time and share common features or properties may be grouped together
2. Closure: sounds that share belongingness will be grouped, such as the example of the cough during a lecture – the cough does not 'belong' to the stream produced by the lecture and is not grouped into that stream
3. Good continuation: sounds that have smooth transitions are likely to be grouped together (this is similar to the proximity principle)
4. Common fate: sounds that come from the same location or coincide in time may be grouped together (such as the orchestra example)
5. Exclusive allocation: this is an important principle for speech perception and states that one may attend to (or allocate neural resources for) one stream or another but not both at one time. This aspect of auditory processing is frequently referred to as selective listening. If one speaker's voice is presented to your two ears in headphones, you have no difficulty in understanding what is being said. If, however, two different speakers' voices are presented simultaneously to your left and right ears, you will only be able to attend to one stream at a time, although you may switch back and forth.

How does the brain perform auditory scene analysis? Investigations of the neural substrates of perceptual organization have led to the formation of several theories of how and where perceptual streaming is

decoded. One view holds that auditory stream segregation involves primary auditory cortex and that the underlying mechanisms for this segregation involve neural suppression of information not contained within an auditory stream (Fishman *et al.*, 2001). A second view holds that auditory stream segmentation exploits cortical change detector mechanisms in detecting aspects of the auditory scene that are not part of a single stream (Sussman, 2005). According to this view, an individual auditory stream is detected based on the acoustic aspects of the auditory sound, such as its frequency and location in space. Once these characteristics are formed into a neural representation of the stream, inputs that do not match this stream are detected using auditory cortical change detection mechanisms. A third view is that the perceptual organization processes take place in an area of cortex that is thought to underlie binding processes for visual and somatosensory input, the intraparietal sulcus (Cusack, 2005). In this view, the perceptual organization of multiple auditory streams occurs external to auditory cortex in neural territory that is implicated in multimodal cortex (Figure 7.21).

The segmentation of an auditory scene into its constituent parts, or streams, is a complex 'problem' for the auditory system to resolve and likely has an equally complex neural basis. Thus, it is not surprising that the neural substrates for auditory scene analysis are still being elucidated in the relatively new field of cognitive neuroscience.

3.3.3 'What' and 'where' processing streams

We have discussed important aspects of auditory perception, including decoding binaural cues to determine *where* a sound is in space and extracting spectral and temporal features to determine *what* that sound is. 'What' and 'where' processing streams have been the topic of many invasive investigations in non-human primates in both the visual and auditory modalities. Converging evidence from these investigations provides evidence of distinct and separable streams for processing 'what' and 'where' information (Figure 7.22).

There is a large and growing body of evidence that cortical networks for decoding what and where information in sound are processed in separate (but highly interactive) processing streams in the human brain. The planum temporale has been suggested to serve as a hub in early auditory cortical processing making contact with two differing streams of processing for decoding spatial location and auditory object identification (Griffiths and Warren, 2002). However, the role of the planum temporale in sound processing is continuing to be elucidated.

Recent neuroimaging studies have investigated processing of where and what information and have shown differing patterns of activity for decoding this

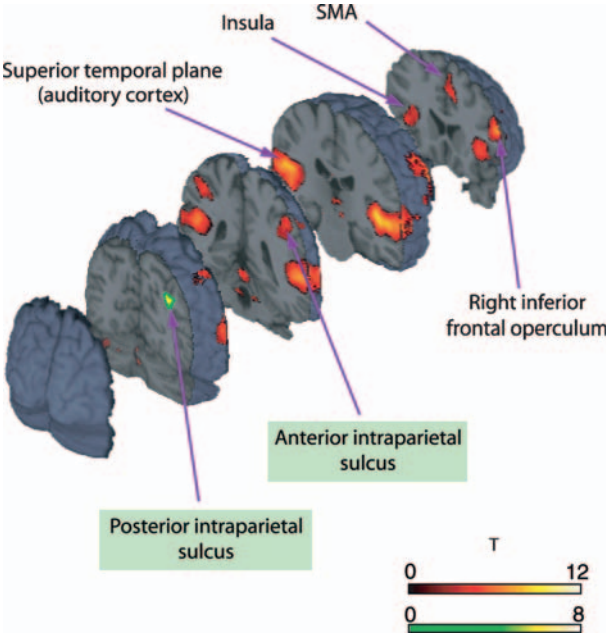


FIGURE 7.21 Cortical areas for auditory stream analysis: region (shown in light green) in the intraparietal sulcus (IPS) when two auditory streams are perceived versus 1. The IPS has been implicated as a region for perceptual organization (binding) of multimodal (vision, touch, sound) information. *Source*: Adapted from Cusack, 2005.

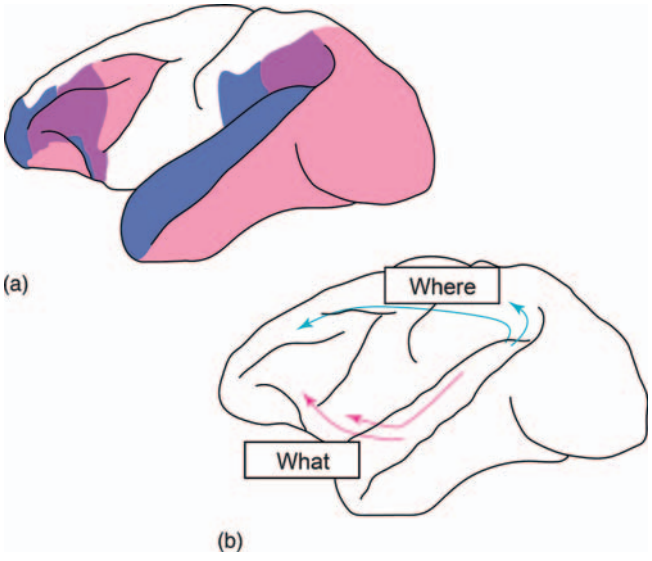


FIGURE 7.22 Auditory regions and streams in the primate brain. (a) The lateral surface of a macaque brain showing regions of visual (pink) and auditory (blue) responsivity. Multimodal responsivity is shown in purple. (b) Two broad 'streams' of processing within the auditory system. *Source*: Adapted from Scott, 2005.

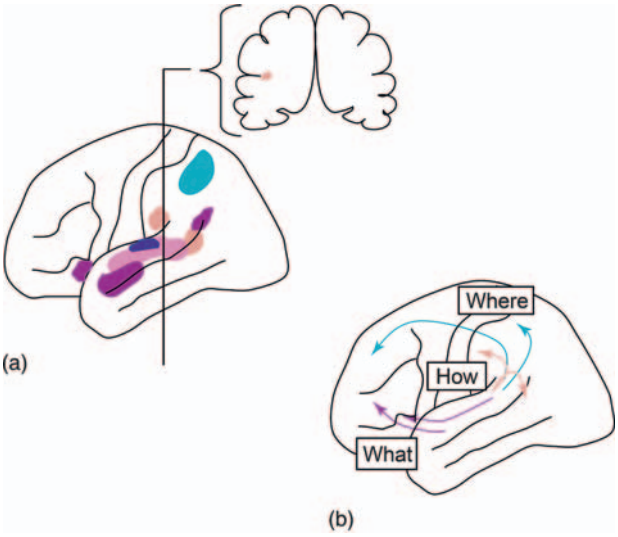


FIGURE 7.23 Functional responses to speech and candidate stream of processing in the human brain. (a) The lateral surface of the human brain: the colored regions indicate broadly to which type of acoustic signal each temporal region (and associated parietal and frontal region) responds. Regions in blue show a specific response to language-specific phonological structure. Regions in lilac respond to stimuli with the phonetic cues and features of speech, whereas those in purple respond to intelligible speech. Regions in pink respond to verbal short-term memory and articulatory representations of speech. Regions in green respond to auditory spatial tasks. (b) The putative directions of the 'what', 'where', and 'how' streams of processing in the human brain. *Source*: Adapted from Scott, 2005.

information. In a recent review article, Scott (2005) provides a summary of findings to date and provides hypothesized brain regions for 'what', 'where', and 'how' processing streams in the human brain (Figure 7.23). However, the functional mapping of cortical auditory processing streams remains an ongoing investigation.

4.0 SPEECH PERCEPTION

Now let's turn to an important area of investigation in the topic of human auditory function: the decoding of speech sounds. Since language is a uniquely human function, it may well be the case that the auditory system in humans differs sharply from those in nonhuman primates. Let's begin our discussion of how we decode human speech with a brief discussion of the units of analysis in speech.

The basic task of the speech system is to map sounds onto meaning. This seems to be a relatively straightforward process: when a speech sound, such as 'd', is heard, the physical sound is mapped onto an abstract representation of that sound, the *phoneme*. The two main types of phonemes are consonants (such as 'd') and vowels (such as 'i'). Individual phonemes are stored in echoic memory while an entire word is being spoken, for example, 'dig'. In order to decode the spoken word 'dig', you might imagine that the neural representations for 'd', 'i', and 'g' are decoded individually and sequentially, and combined to map onto a sound representation of the word 'dig'. The result is that the word 'dig' is activated in the semantic/conceptual knowledge system. Unfortunately, this description makes perfect sense but it is not how the speech system actually works. In fact, there is little agreement in the field of speech perception regarding the basic 'building blocks' of speech: is an individual phoneme the smallest unit of analysis for speech systems? Or is the syllable the appropriate unit? We will return to this question later in the chapter. For now, consider that the speech system must not only decode the individual phonemes in speech to map the sound information to meaning, but it must also decode 'who' information in order to know who is speaking and 'when' in order to understand the temporal order of speech phonemes, syllables, words, and sentences. As mentioned earlier in the chapter, the speech signal must be evaluated across multiple time scales (20, 200, 2000 ms, see Figure 7.2). This information must be decoded accurately regardless of the differences in human speech: whether we hear a high-pitched voice of a child or a low-pitched voice of a man, whether we are speaking very loudly or whispering, or whether we are speaking quickly or slowly. Obviously, the speech system is doing a lot more than a simple mapping of sound onto meaning and it cannot rely solely on the physical aspects of speech since they vary so widely both within and across speakers. Despite the intricacies of speech perceptual processes, they occur with little attention or apparent effort on our part. Let's begin with a little history of speech science.

4.1 Background and history

Research into how speech is decoded is a relatively young area of investigation. While scientists have long studied language in the brain and investigations of the physical properties of sound date back to the early 19th century, the specific study of how acoustic signals map onto meaning is relatively new. Speech perception investigations began during the pre-World War II era. Several events combined to move the study of speech perception into the forefront. First, prior to and during World War II, there was a need for developing speech recognition systems for covert war-related

BOX 7.1 From vocoder to bionic hearing

The technology underlying early vocoders remains in active use today and forms the basis for the way in which cochlear implants stimulate the auditory system to provide hearing for individuals with certain kinds of hearing losses (see Figure 7.24).

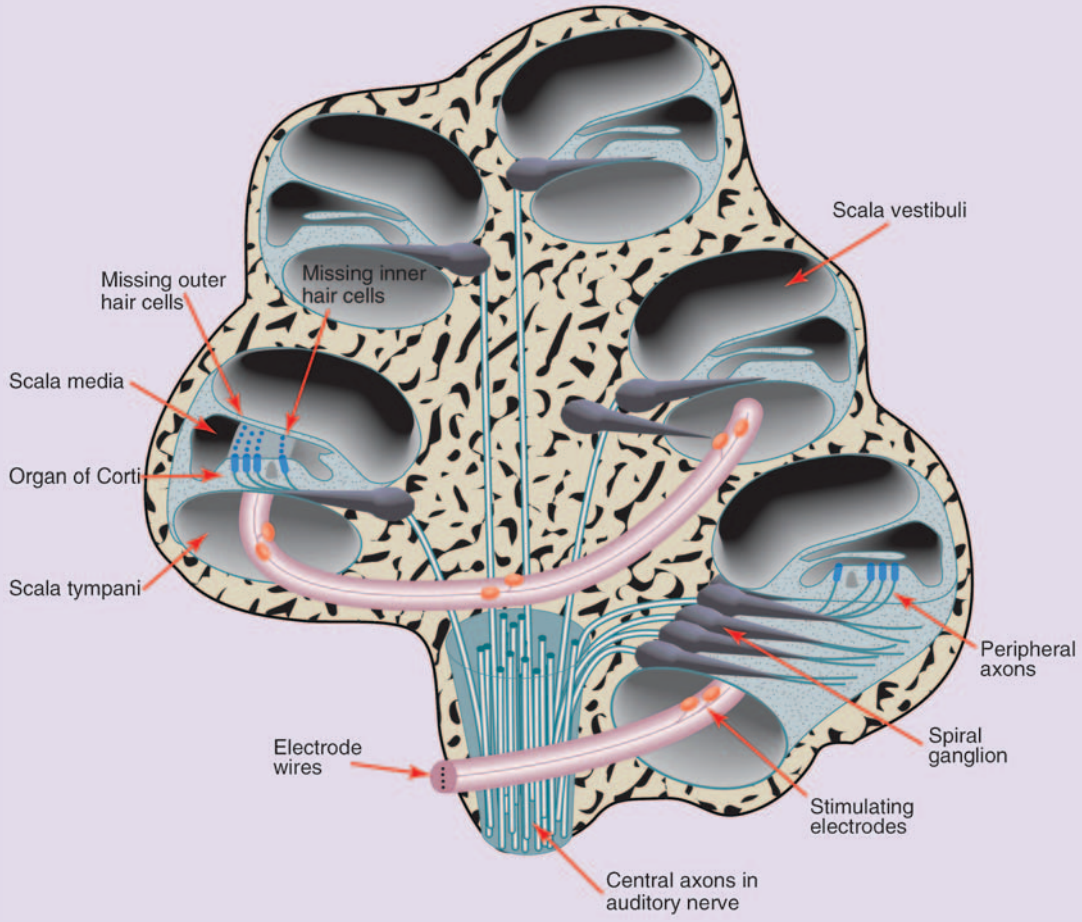


FIGURE 7.24 *Source*: Brown, 2003.

communications. Next, two inventions changed the way we thought about and studied human speech. First was the *vocoder* (voice + coder) developed by Homer Dudley of Bell Telephone Laboratories (Dudley, 1936). The vocoder provided a method to transmit speech signals over long telephone circuits by analyzing and recoding speech into simpler signals that contained far less information than natural human speech. The outcome was a far simpler speech signal that was, nonetheless, quite understandable, providing evidence that the speech signal contained many redundant features. These findings launched experiments to determine what was the minimal information required to comprehend speech.

A second invention was actually developed during World War II but kept secret until after the war ended: the *spectrograph*. The spectrograph was also developed by scientists at Bell Labs and was based on some of the principles Dudley developed during the making of the vocoder. The spectrograph analyzed the sound signals and produced a picture called a *spectrogram* (Figure 7.25) or visible speech (Potter *et al.*, 1947).

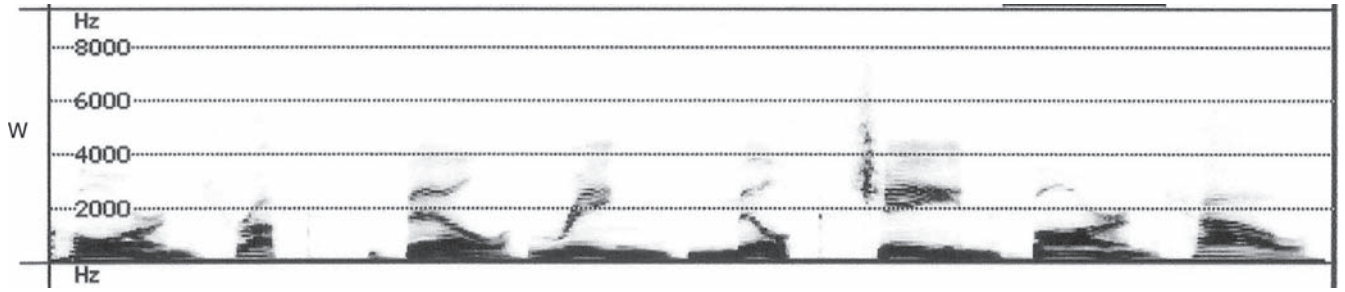


FIGURE 7.25 Spectrograms of individual spoken words. Time is depicted on the x-axis and frequency is depicted on the y-axis. Darker shadings indicate higher amplitude, mostly contained in the formants within each speech sound. *Source*: Adapted with permission from Binder *et al*., 2000.

In a spectrogram, frequency of the speech signal is presented on the y-axis and time on the x-axis. The shading of the speech signal represents a third dimension, intensity (or energy). Intensity is presented in two ways: across time (x-axis) and within frequency (y-axis). In this way, the amount of intensity or energy can be represented both as a function of time during a sentence and as a function of frequency band within a spoken syllable or word. No shading (white areas) in regions of the spectrogram along the x-axis indicates silence at those points in time. No shading in regions up and down the y-axis, within each speech sound, indicates no energy at that frequency. Similarly, darker shading along the y-axis indicates more energy at that frequency band. You will note that each speech sound presented in Figure 7.25 has regions of darker shading at fairly narrow frequency bands: these are the *formants* that occur in human speech. Formants occur at fairly regular intervals and are produced by air that oscillates as it ascends through the vocal tract. The formants or harmonics differ by individual, based on the size of the vocal tract. The spectrograph radically changed how speech perception was investigated and provided a method for scientists to evaluate substructural elements of the speech signal in a way never before possible.

There were two important outcomes of early investigations of speech using spectrograms: first, spectrograms of sentences showed that gaps or silences within sentences did not map onto word boundaries, but occurred within words in many cases; and second, inspection of the detailed information for individual phonemes showed that the formant structure for phonemes, such as /d/, differed sharply depending on the following vowel (Figure 7.26).

These two findings had important ramifications on models describing how the brain decodes speech. First, gaps or silences in the speech stream do not provide the speech decoding system with information about when a word begins or ends. Clearly, the speech system needed to use other cues for word recognition. Second, individual phonemes in speech were physically quite different depending on the phonemes that occurred just before and after them. This *lack of invariance* implied that there were no simple sound templates in the brain that mapped in a one-for-one basis to phoneme identities.

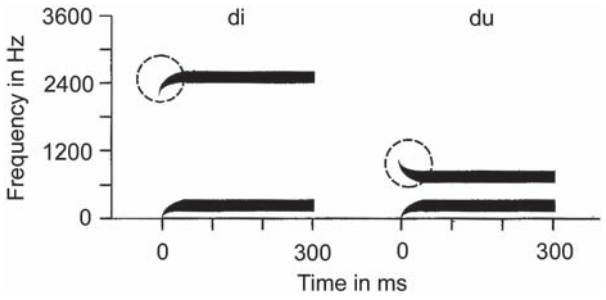


FIGURE 7.26 Schematic illustration of the direction and frequency of formant onsets in the syllables /di/ and /du/, demonstrating that, although the percepts of the two syllables beginning with the sound 'd' will map onto a single phoneme /d/, the physical instantiations of the initial /d/ are quite different. *Source*: Carroll, 1999, originally from Liberman, 1970.

Despite these complexities regarding how speech is decoded, spectrograms enabled speech scientists to describe pictorially important features in phonemes, such as where in the speech articulation system they are produced (place of articulation) and the duration of the onset of vocal cord vibration (voice onset time). Consonants could now be categorized according to these *distinctive features* (Figure 7.27).

4.2 Early theories of speech perception

An important outcome of early speech science was the realization that the physical features in individual

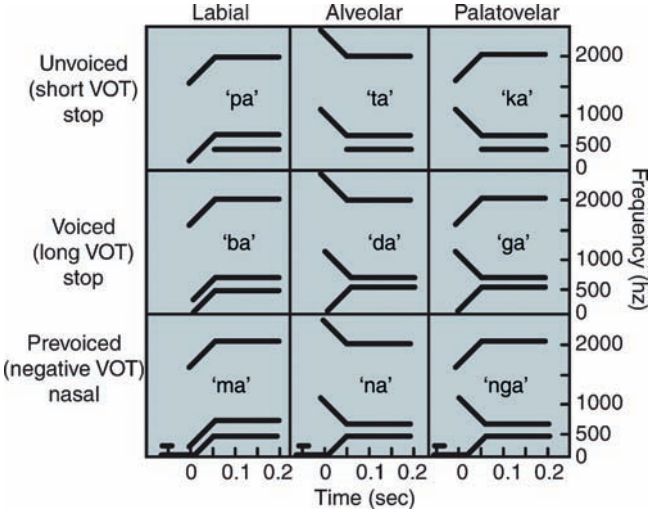


FIGURE 7.27 Schematic illustrations of the formant patterns for distinctive features in classes of speech sounds. *Source*: Brown, 2003.

speech sounds or phonemes did not provide invariant information for their decoding. Recall that the work of Fourier and Ohm provided a basis for deconstructing complex sounds into simpler sinusoidal parts. The findings of lack of invariance in speech sounds indicated that speech decoding systems must be quite different from those for decoding other types of sounds. That is, if speech perception did not entail an analysis of the sum of the physical parts, and it clearly could not because the physical parts vary widely for a single phoneme, then how was it performed? One theory was that the neural systems for speech decoding were specialized and not part of the general auditory system. A strong view of this theory that 'speech was special' held that the special systems for speech decoding occurred as early as the ear (Liberman *et al*., 1967). The lack of invariance finding led Liberman and colleagues to develop the *motor theory of speech perception* (for a review, see Liberman and Mattingly, 1985). This theory suggested that speech perception was tightly coupled to speech production, specifically the motor articulation processes or gestures used in producing speech. While the acoustics of phonemes lack invariance, the motor theory held that the articulatory gestures used to produce them were invariant and the neural representations of these gestures were accessed in speech perception. Other theories for speech perception have been developed since the motor theory, and this work is ongoing in speech science, with the underlying notion that the speech system must have a way to maintain a perceptual constancy across a wide variety of physical features in phonemes and words.

A central debate in speech perception science has raged since the work of Liberman and colleagues during the 1950s and 1960s: the 'speech is special' view holds that speech and language processes are encapsulated within a specific language system, i.e. they are *domain-specific* (where the domain is language). An alternative view is that speech and language processes exploit brain systems in use in general cognition, i.e. they are *domain-general*. For speech perception, early work by Tallal and colleagues provided evidence that left lateralized language processing was not due to domain-specific language organization in that hemisphere but, rather, was due to a domain-general auditory processing bias in the left hemisphere for decoding rapidly changing temporal features in sounds, such as those contained in speech (for a review, see Tallal, 2001). These two opposing viewpoints are still the topic of ongoing discussion and have not yet been resolved. However, it is likely that the neural systems for decoding speech have a combination of domain-specific and domain-general processing.

4.2.1 Units of analysis – the building blocks for the speech system

What are the basic elements or units for decoding speech? Is it the phoneme? The syllable? The early findings of a lack of invariance in phonemes provide evidence against the phoneme as the best unit of analysis for speech perception, although phonemes are clearly critical elements in speech perception. Speech contains multiple cues, however, and so it is perhaps not surprising that a simple one-to-one mapping of phonemes to words does not provide a full description of the processes underlying speech perception (see Scott and Wise, 2004, for a review). Recall that the auditory system is not a uni-directional system, but has complex feedback systems that extend all the way to the cochlea as well as parallel interactive systems across cortical regions within auditory cortex, across the hemispheres, and extending to other sensory and memory systems.

These complex processing pathways clearly aid in decoding the speech signal. The syllable as a basic unit of speech makes some intuitive sense because of the lack of invariance issue as well as the importance of decoding syllabic stress when mapping sound onto meaning. For example, the words 'melody' and 'melodic' are very similar in terms of the sequence of the phonemes. However, the syllabic stress differences in the two words lend an important cue to understanding

their meanings. Nevertheless, the field of speech science has not agreed upon an answer to the question of what is the best unit of analysis for understanding speech and this issue must remain unresolved here.

4.2.2 Minimal information for decoding speech

Since the speech signal is so complex with many overlapping cues, perhaps a better way to understand how speech is encoded is to investigate what is the minimal information required to comprehend speech? This approach was taken by Shannon and colleagues (Shannon *et al*., 1998) with the central idea that the 'shape' of the speech signal, i.e. the rising and falling fluctuations over time, or *temporal envelope*, carries the minimal information required for decoding speech. Shannon presented degraded speech that had no frequency information but differing levels of temporal information. Listeners were able to decode continuous speech with remarkable accuracy, indicating that while frequency information is obviously important in decoding speech, it is not necessary. Shannon's work provided evidence that the temporal envelope of speech might carry more relevant information for its decoding than the fine-grained features found in phonemes.

The lack of general agreement regarding the basic building blocks of speech in the field of speech science makes the investigation of the neural bases of speech perception somewhat more difficult! Nevertheless, there have been many studies of how speech and other classes of sounds are decoded in the brain and we highlight some of these here for you in the following section.

4.3 Functional mapping of speech-specific processes

Early neuroimaging studies by Binder and colleagues (for a review, see Binder, 1997) investigated stimulus-based differences in auditory cortex by comparing brain activation in response to speech sounds (words) versus tones or noise. A general finding was more widespread activation in superior temporal gyrus and the superior temporal sulcus for words as compared to the tones or noise. Although these results could be interpreted as representing speech-specific processing in those auditory regions, they were difficult to interpret, however, because words and the non-speech sounds (tones, noise) differed not only in terms of representing speech versus non-speech classes of sounds, but also in their complexity. Therefore, different brain activation patterns might reflect speech versus non-speech functional areas, but might also reflect areas that differ in terms of decoding complex features in sounds.

A recent investigation addressed these issues with the presentation of many classes of sounds, including noise bursts, tones, words, pseudowords (pronounceable non-words, such as 'hig', and reversed speech (Binder *et al*., 2000). The aims of this study were to investigate auditory cortical regions that were activated for speech versus non-speech, and compare regions that were activated for words versus pseudowords versus reversed speech (Figure 7.28).

The major findings were that Heschl's gryus and the planum temporale were activated similarly for all sound stimuli. This result supports the notion that sound is processed in a hierarchical fashion, with Heschl's gyrus showing activation for all classes of

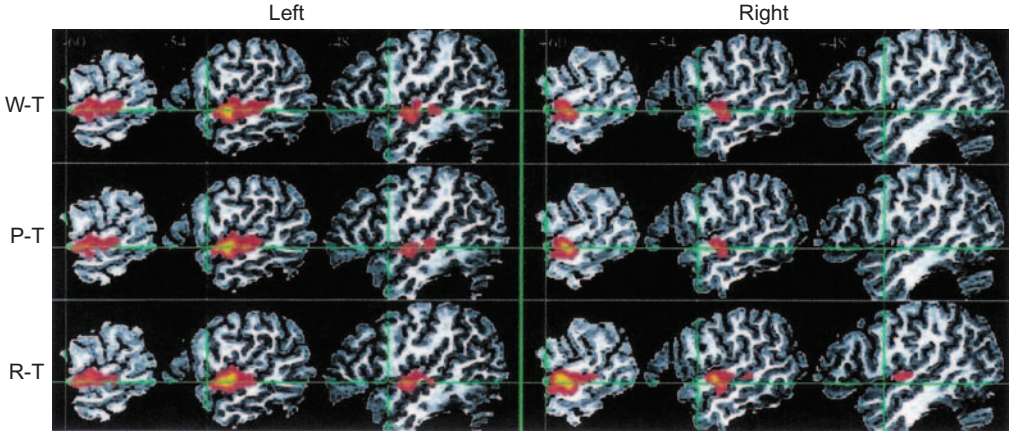


FIGURE 7.28 Comparison between three Speech-Tones contrasts (Word-Tones (W-T), Pseudowords-Tones (P-T), and Reversed-Tones (R-T)). Areas responding more to speech than to Tones are very similar for all contrasts. *Source*: Adapted from Binder *et al*., 2000.

sounds and likely representing an early sensory analysis. Speech sounds activated a larger region of auditory cortex than the non-speech sounds, extending into the posterior superior temporal gyrus and the superior temporal sulcus. Interestingly, the activation did not differ for words, pseudowords, and reversed speech. These findings indicate that speech activates a larger-scale network of auditory cortex than the simpler noise bursts and tones. Because there were no differences between the words, pseudowords, and reserved speech conditions, Binder and colleagues concluded that these regions likely do not reflect semantic processing of the word meaning, but reflect phonological processing of the speech sounds.

There are many active lines of investigation into the neural mechanisms and regions employed in decoding human speech and this work is ongoing. Let's move ahead to a discussion of the relationship between 'hearing' and 'saying': speech perception versus production.

4.4 The link between speech perception and production

Early neuroimaging studies investigated brain activation for hearing versus producing speech. One important finding that has been reproduced many times is that auditory cortex is activated during speech production tasks as well as during the perception of speech (Figure 7.29).

Why is auditory cortex active during speech production? Is it simply the case that while producing speech, we hear our own voice? Or does the auditory system play a role in speech production? There is evidence from neuroimaging studies, as well as from lesion studies with patients with aphasia, that speech perception and production systems are tightly coupled. From infancy, as speech and language are acquired, there are complex interactions between heard language and spoken language which guide the development of language. In fact, Carl Wernicke proposed a model for language processing in the late 19th century that included a pathway from auditory speech perception areas to motor speech production areas and proposed that the 'sound images' of words would serve to constrain the output when producing words. This model remains in use today, and while we know more about dynamic brain processes now than during Wernicke's time, the model has provided an important theoretical framework for studying human language systems.

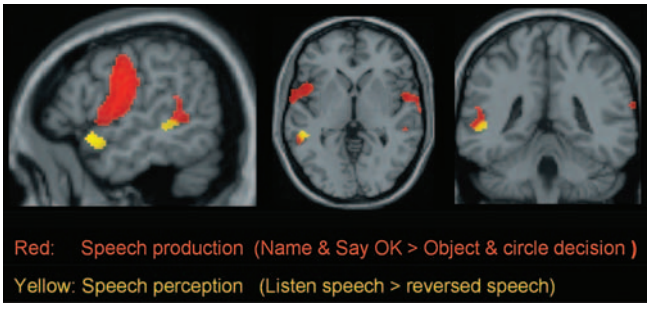


FIGURE 7.29 Red shaded areas show activation for speech production while yellow shaded areas show activation for listening to speech. *Source*: Adapted from Frackowiak, 2004.

4.4.1 Inner speech

What about brain areas for speech production when actual speech is not actually produced, when we talk to ourselves? The investigation of brain areas involving inner speech provides an intriguing way in which to study our own consciousness. In a recent article, Hesslow (2002) addressed this issue and proposed a simplified model of brain areas that may be employed for inner speech (Figure 7.30).

While there are clearly complex interactions between brain areas for decoding speech and producing speech, theorized in early motor theories of speech perception and realized in later brain studies, the exact nature of the integrative processes and neural territory that are shared during listening versus producing speech are still being elucidated in the field of human language research.

4.5 Damage to speech perceptual systems

Prior to the advent of neuroimaging, much of what we learned about brain systems for decoding speech came from investigations with individuals who had brain damage, typically due to a stroke since they produce damage that is more limited in brain area than, for example, a closed-head injury. Strokes, nevertheless, can vary widely in the amount of brain area affected. The result of the stroke is a blockage of blood flow, which causes neuronal death and produces a lesion. The lesion in the area affected by the stroke, in turn, produces behavioral symptoms due to the brain damage. When a stroke patient has impaired language function, it is called *aphasia*. Patients with aphasia have widely varying symptoms depending on the location and the size of their lesion. Two basic classifications of aphasia

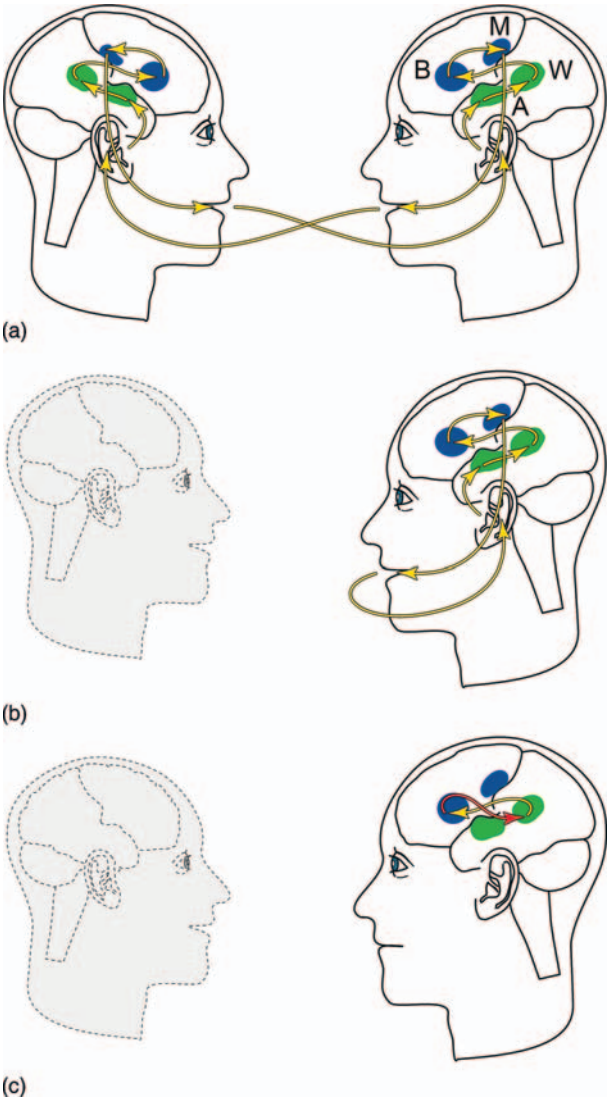


FIGURE 7.30 Internal simulation of conversation. (a) We can respond to a question without being conscious of our behavior. The verbal signal enters the primary auditory cortex (A) and then Wernicke's area (WA). This will elicit formation of a reply in Broca's area (B) and the primary motor cortex (M). (b) We can also listen and respond to our own talk using the same brain regions. (c) If the preparation of the verbal response can be fed directly (red arrow) into auditory cortex or Wernicke's area, we can also speak silently to ourselves using essentially the same mechanisms. *Source*: Adapted from Hesslow, 2002.

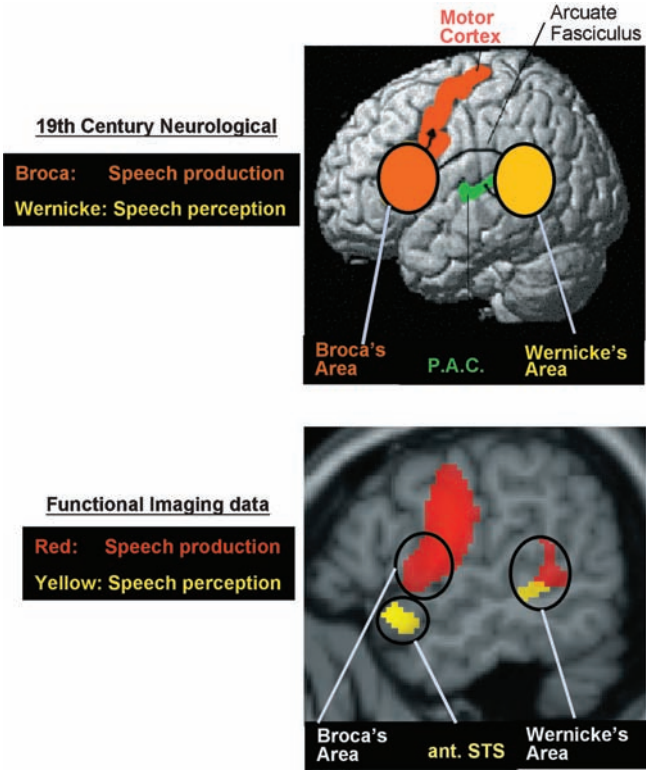


FIGURE 7.31 Upper panel shows classical language areas adapted from 19th century neuroanatomists. Lower panel shows contemporary view of the classical models. *Source*: Adapted from Frackowiak, 2004.

come from 19th century neuroanatomical investigations of brain areas for language: Paul Broca discovered a region in the inferior frontal lobe that was important for speech production, and Carl Wernicke discovered a region in the temporal lobe that was important for speech perception. Damage to these regions would produce aphasia with symptoms that differed depending on which area was affected: an individual whose major symptoms are impaired speech production is classified as a *Broca's aphasic*, an individual whose major symptoms are impaired speech comprehension is classified as a *Wernicke's aphasic* (Figure 7.31).

Blumstein and colleagues (for a review, see Blumstein, 1997) used careful testing to determine which aspects of speech comprehension were affected in aphasia. One series of experiments was designed to determine if speech comprehension problems were due to damage to speech perceptual processes for mapping the acoustic sound onto abstract phoneme representations (*phonemic deficit*) or if they were due to word recognition processes for mapping the phonemes onto meaning (*semantic deficit*). Blumstein used an auditory word-to-picture matching task to test the aphasic patients. In this task, the patient hears a word and must point to the picture that matches the word. The picture choices include a picture of the word that was heard (the target) and three incorrect choices (foils): one foil is similar in its sound (phonemic), one is similar in meaning (semantic), and one is unrelated to the target word in either sound or meaning. In Figure 7.33, we recreate this experiment: the

BOX 7.2 A new look at a classical model: tractography reconstructions of language pathways

Recent developments in neuroimaging have provided us with new ways to visualize the brain. One major neural 'highway' of the brain that has long been of interest to language researchers is the *arcuate fasciculus*: this large fiber tract connects the anatomical regions that correspond to the functional Broca's and Wernicke's areas in the left hemisphere. Disruption of this pathway was thought to be the underlying cause for a type of acquired language impairment (aphasia) called *conduction aphasia*. However, when carefully tested, individuals with a diagnosis of conduction aphasia show a wide array of symptoms, raising the question of whether a single type of neural damage produced them.

Researchers Catani and colleagues used diffusion tensor tractography to reconstruct the three-dimensional pathways of white matter tracts that course between Broca's and Wernicke's area (Catani *et al*., 2005). They found evidence for the white matter tract known as the *arcuate fasciculus* that formed a direct pathway between Broca's and Wernicke's areas, shown in red in Figure 7.32. However, they also found an *indirect pathway* that runs side-to-side (laterally) with an anterior segment (shown in green in Figure 7.32) that connects Broca's area with a region in the inferior parietal cortex that is known as Geschwind's territory and a posterior segment (shown in yellow) that connects Geschwind's territory and Wernicke's area.

Although this new finding awaits replication, it may well be the reason that conduction aphasia patients show such differing ranges of symptoms: if parallel direct and indirect pathways connect Broca's and Wernicke's areas, then language disruption would differ sharply depending on which pathway and where in that pathway the damage has occurred.

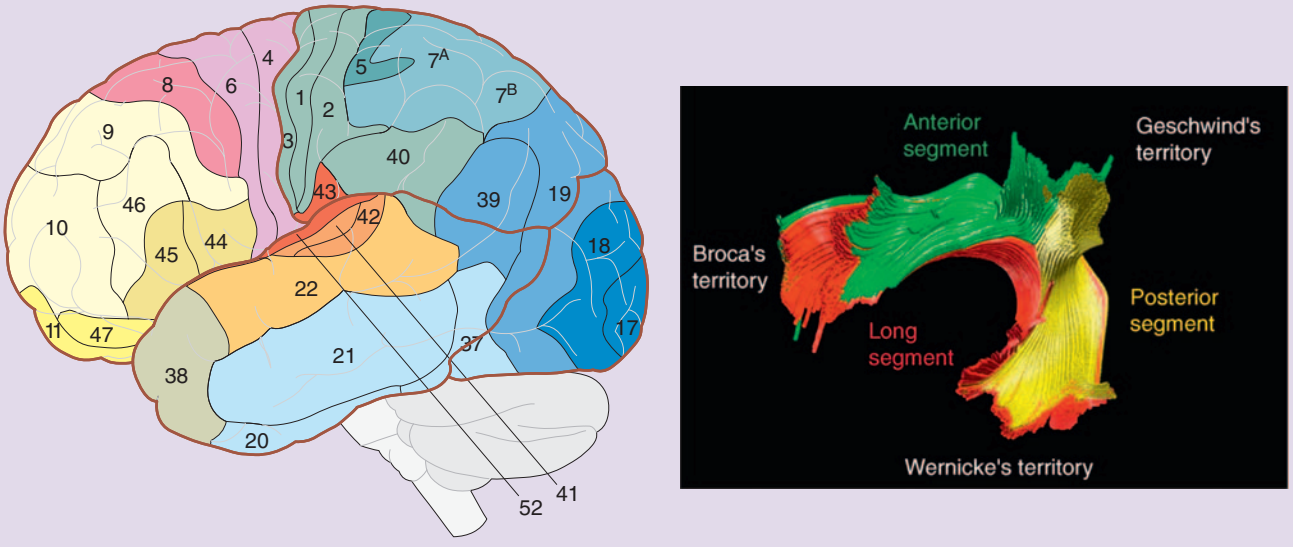


FIGURE 7.32 Right panel shows the fiber tracts that connect the functional language areas of Wernicke's area in the temporal lobe and Broca's area in the frontal lobe in the left hemisphere. These tracts are reconstructed using tractography and MRI images. A direct pathway between Broca's and Wernicke's areas, shown in red, corresponds to the classical description of the arcuate fasciculus that has been long thought to be the major connective 'highway' between these important language areas. They also found an indirect pathway: the anterior segment connects Broca's area with a region in the inferior parietal lobe known as Geschwind's territory (shown in green) and a posterior segment that connects Geschwind's territory and Wernicke's area (shown in yellow). Left panel shows where these tracts are relative to the anatomical structures of the left hemisphere. *Source*: Adapted, with permission, from Catani *et al*., 2005.

left panel shows examples of target words 'keys' and 'peas' which differ in the place of articulation of the initial consonant but otherwise share distinctive features (voicing: they are both voiceless, manner: they are both stop consonants). The right panel shows representational picture choices, with a semantic foil (carrots) on the top left, an unrelated picture on the top right, a phonemic foil (keys) on the bottom right, and the correct choice, peas, on the bottom left.

The pattern of errors (pointing to the incorrect picture) made by the patient provides information about which decoding processes are damaged. If the patient makes mostly phonemic or sound-based errors, then the inference is that processes underlying the

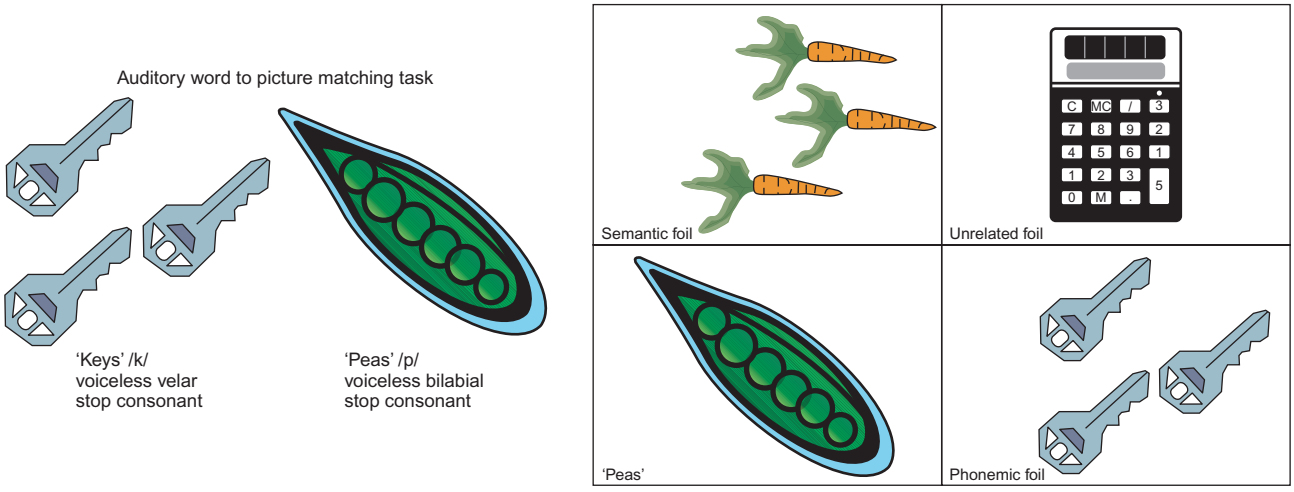


FIGURE 7.33 Left panel illustrates the minimal pairs of words that have initial consonants that differ in a single distinctive feature. In this case, the initial /k/ and /p/ differ in place of articulation (velar versus bilabial) but are matched for voicing (voiceless) and manner (stop consonant). Right panel depicts the stimuli used for a single trial in an auditory-word-to-picture-naming task. The subject hears a word, in this case 'peas', and is asked to point to the picture that matches the word. Upper left panel shows a meaning-based (semantic) foil, upper right panel shows an unrelated foil, lower left panel shows the correct (target) response, and lower right panel shows a sound-based (phonemic) foil.

mapping of acoustic sound onto phonemes are impaired. On the other hand, if the patient makes mostly semantic errors, the inference is that sound mapping processes are intact and the speech recognition problems are due to impairments in systems for mapping phonemes onto meaning. Two important results of these investigations are that the pattern of errors made by patients did not correspond in a meaningful way to their aphasia classification: for example, one might suppose that Wernicke's aphasics would make many more phonemic errors, due to damage in speech comprehension brain areas, than Broca's aphasics. This was not the case, however. The second important result was that all aphasics – Broca's and Wernicke's – did quite well on this task. The conclusion drawn was that speech perception, the ability to map the acoustic features of a sound onto representational phonemes, is largely intact in aphasia. The deficits in comprehending speech, therefore, are not due to sound-based impairments. These and other investigations of brain areas that subserve speech perception provide evidence that, while language function tends to be lateralized to the left hemisphere in most right-handed individuals, speech perceptual processes may be organized bilaterally, i.e. in both hemispheres.

Subsequent studies have provided further evidence to support this conclusion: in order for an individual to show severe speech perception impairment (called 'pure word deafness'), brain damage must include lesions in both hemispheres or lesions in the left hemisphere that include damage to the corpus callosum, prohibiting right hemisphere information flow to the left (see Poeppel, 2001, for a review).

4.6 A working model for speech perception in the brain

For most right-handed individuals, language is lateralized to the left hemisphere. The language system is not unitary, however, and includes many computational stages from decoding the speech sounds to form an abstract representation, to making contact with semantic and grammatical systems, to producing speech. A recent model of the auditory language system proposes that early speech decoding processes are organized bilaterally in left and right auditory fields while later semantic/syntactic processes are organized in the left hemisphere (Figure 7.34) (Hickok and Poeppel, 2007).

While we have learned a lot about how speech is processed in the brain, through neuroimaging studies with healthy individuals and neuropsychological studies of individuals with brain damage, our understanding of how speech is perceived is still an ongoing investigation. Perhaps this is not surprising since speech perception scientists have not agreed upon the basic units of analysis for speech perception! New techniques, such as TMS, and innovative experimental designs are providing new data for understanding how we decode speech and where in the brain these systems are located.

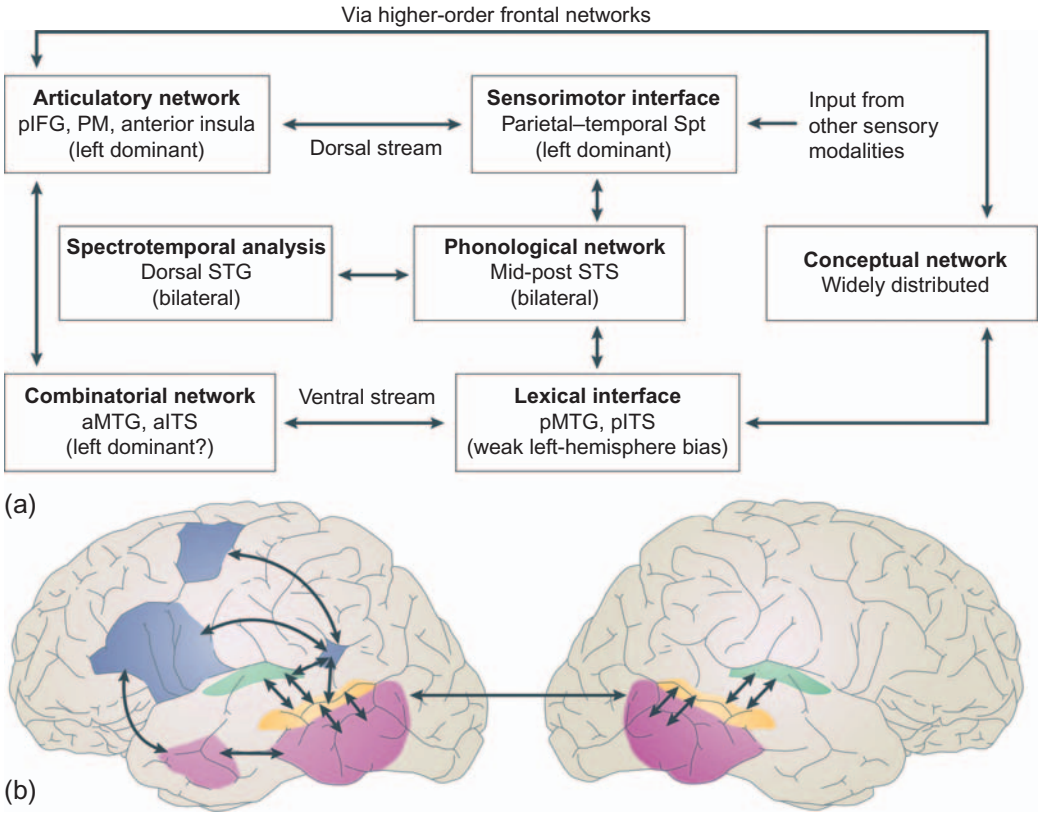


FIGURE 7.34 (a) Shows a schematic for the model of auditory language processing proposed by Hickok and Poeppel, 2007. (b) Shows brain regions proposed to reflect stages of the model. Note that early speech perceptual systems (shown in green and yellow) for mapping the acoustic-phonetic information in sounds onto meaning are proposed to be mediated bilaterally in left and right hemispheres while later processes are proposed to be mediated by left hemisphere regions. *Source*: Adapted from Hickok & Poeppel, 2007.

FRONTIERS OF COGNITIVE NEUROSCIENCE

Music and the brain

FIGURE 7.35 Aniruddh D. Patel, PhD, Neurosciences Institute, San Diego, CA, USA. *Source*: Tom Cogill.

Music, like language, occurs in every human culture and extends deep into our species' past. The oldest known musical instruments, flutes made from bird bones and mammoth tusks, are over 35 000 years old (Conard *et al*., in press). Although the power of music in human life has fascinated thinkers since Plato, only recently has research on music and the brain really begun to flourish (e.g. Peretz & Zatorre, 2003).

Several basic facts are already apparent. First, the study of brain-damaged patients with altered music perception has shown that music is a highly complex cognitive system with many distinct subcomponents (Stewart *et al*., 2006). Second, neuroimaging research with normal individuals has shown that listening to or making music engages much of the brain (not just the auditory areas), even in people with no formal musical training (Koelsch *et al*., 2005). Third, learning to play an instrument affects brain structure and function at both the subcortical and cortical levels, and improves nonmusical cognitive

FIGURE 7.36 Snowball, a medium sulfur-crested cockatoo (*Cacatua galerita eleonora*) that synchronizes to the beat of human music (Patel *et al*., 2009). *Source*: Irena Schulz.

functions (Schellenberg, 2005; Wong *et al*. 2007; Hyde *et al*., 2009). Fourth, music processing represents an intimate relationship between cognition and emotion (Huron, 2006; Steinbeis *et al*., 2006).

As with any other branch of science, research on music and the brain often is driven by debates. One debate in which I have been involved concerns the issue of "modularity"; that is, the extent to which music uses dedicated brain circuitry vs. shared processing mechanisms with other cognitive domains, such as language (Peretz, 2006). Music clearly involves a certain degree of brain specialization, but my work and that of several colleagues suggest that music and language processing overlap to a surprising degree (Patel, 2008). This has implications for a number of issues in cognitive neuroscience, including the study and treatment of language disorders (Patel *et al*., 2008; Schlaug *et al*., 2008).

Another active debate concerns evolution. Did human music evolve as a biological adaptation because it helped our ancestors survive? Or is music a human invention, based on brain mechanisms that evolved to serve other functions? These questions can easily lead to armchair speculation, but one recent trend has been to take these questions into the lab by doing cross-species research on music perception (Hauser & McDermott, 2003). For example, my lab recently demonstrated that a nonhuman animal can move to the beat of human music (Patel *et al*., 2009; see Figure 7.36). This suggests at least one fundamental aspect of music cognition does not require brain circuits shaped by natural selection for music.

A major question for future research is also one of the oldest questions about music: why does it have such emotional power for humans? The biological basis of our emotional responses to music are just beginning to be explored (Juslin & Västfjäll, 2008), and exciting discoveries will be made in the years ahead.

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5.0 MUSIC PERCEPTION

Like speech perception, music perception is uniquely human. There are many similarities in speech and music perception: music has complex phrase structures and its perception involves the mapping of sound onto meaning (and emotion). Music perception allows for the recognition of melodies despite differences in instruments, keys, and tempos; thus it cannot be a system built on absolutes but must have relative representations. Thus, music perception systems must have the ability to maintain a perceptual constancy in music representation. A central difference between speech and music perception is that all typically developing humans master speech perception. We are not only good at speech perception, we are masters! This is not the case in music perception: there is tremendously more variability in music perception abilities and significantly more explicit learning that goes along with musical acuity. The variability in music perception abilities combined with the many levels of musical training and skill has made the study of music perception difficult because of these inherent individual differences. These difficulties, however, provide a unique opportunity in that they provide an opportunity to understand the effects of learning and plasticity in the brain areas that decode music.

5.1 Stages of music processing

The perception of features in music involves many stages of processing within the auditory system as well as across brain regions (Figure 7.37) (Zatorre, Chen, and Penhune, 2007). This processing must include feedback as well as feedforward systems as well as making contact with stored memories and experiences as well as emotional systems. Music perception is quite different from speech perception in that many musical signals do not contain any lyrics. Thus, the music perception processes likely have a more abstract (non-linguistic) representational basis.

While the music signal is complex, like all sound, music has basic physical elements: frequency, intensity, and time. The psychological aspects of frequency and time in music correspond to pitch (melody) and temporal structure (rhythm). Traditionally, melodic and temporal aspects of music have been investigated as separate features of music perception. However, they likely are not completely independent. Just as some speech scientists propose that speech may be processed in brain areas specialized just for speech, music scientists have theorized that there may be neural systems specialized for music. Evidence in support of music-specific systems in the brain has been provided in neuropsychological studies with patients who have suffered brain damage. Peretz and colleagues have provided a series of investigations with brain damaged individuals showing that, in some individuals, pitch or melody perception may be selectively damaged, leaving temporal structure perception intact, while in other individuals temporal perception may be damaged while pitch perception is intact. These findings have led to the development of a model for the brain organization for music perception (Peretz and Zatorre, 2005), where melodic features in music are processed preferentially in the right hemisphere and can be selectively impaired with right hemisphere brain damage, whereas temporal structure in music is decoded in a larger network of brain areas in both hemispheres.

5.2 A separate system for music perception?

Is music perception a separable aspect of auditory processing? While the work of Peretz and colleagues provides compelling evidence that this is the case, a recent review (Koelsch, 2005) of neuroimaging studies of music perception describes a growing body of evidence in support of the view that some aspects of music perception, notably the musical structure or syntax and the musical meaning or semantics, share neural territory with brain areas for language processing (Figure 7.38).

While there is ample evidence from the work of Peretz and colleagues (see Peretz and Zatorre, 2005, for a review) that music perception may be selectively – and differentially – damaged with lesions in left or right hemispheres, the studies reviewed by Koelsch (2005) provide compelling evidence for at least some shared systems in music and language processing. Language and music are both uniquely human and highly structured signals, with multiple dimensions along spectral and temporal axes for understanding their basic and complex structures. Perhaps there is no unitary brain region for either language or music: it may be the case that language and music systems have some neural territory that is specific for their processing and some neural territory that is shared. Complicating an already complicated issue are the differing amounts of musical training and levels of expertise among humans, musicians, and non-musicians.

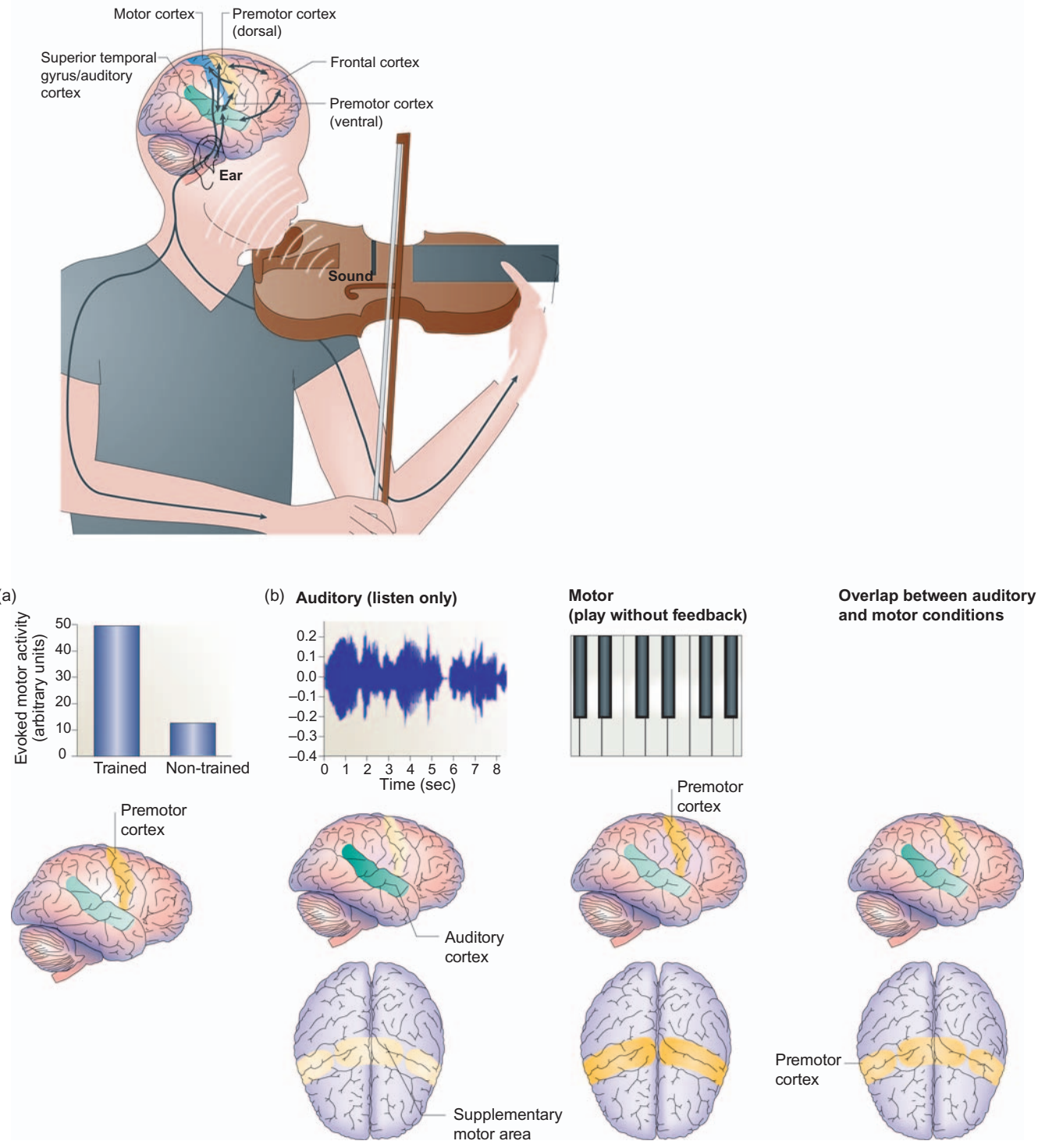

FIGURE 7.37 *Top panel*: Have you ever wondered what areas of your brain 'light up' when you play or hear music? Of course, the auditory regions do activate when you play an instrument, for example, but so do many motor regions involved in the production of the sound from the instrument. In fact, these motor and sensory (auditory) systems are tightly coupled and together form a neural circuitry that provides feedback and feedforward information for musical instrument playing. *Bottom panel*: Results from several neuroimaging studies provide evidence for a tight coupling between activity in auditory and premotor cortex: (a) People without musical training were taught to play a simple melody on a keyboard and their brain activity for listening to that melody was compared in pretraining vs. posttraining scans. Results showed activity in auditory cortex, as expected, when listening to the melody, but there was also activity in the premotor cortex but only in the posttraining condition. (b) In other studies, researchers compared the brain activity of musicians while they listened to a piece they knew how to play (left column) with the brain activity while they played the same piece but without auditory feedback (middle column). There was significant overlap in the premotor cortex and in auditory cortex, suggesting that auditory and motor systems interact closely during both perception and production. *Source*: Zatorre *et al.*, 2007.

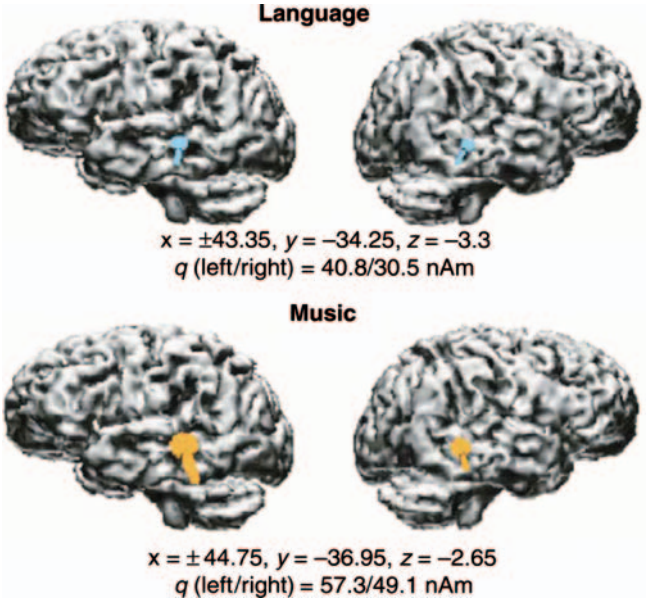

FIGURE 7.38 Top panel shows brain areas active for language. Bottom panel shows brain areas active for music. *Source*: Adapted from Koelsch, 2005.

6.0 LEARNING AND PLASTICITY

A central theme in the study of human cognition has been the investigation of how new information is encoded in the brain during *learning* and how the brain adapts and reorganizes to new situations or, following damage, *plasticity*. These issues are of theoretical value in understanding brain function but also have important practical relevance. One key question is how the auditory cortex responds to deprivation of sensory input due to acquired hearing loss, neural damage, or deafness. For example, if a child is born profoundly deaf and is fitted with a cochlear implant at age 2, will his auditory cortex be receptive to sound and will he hear normally? Or will the 2 years of no exposure to sound limit the effectiveness of the implant? These and other questions regarding cortical plasticity are under intense investigation by auditory scientists.

6.1 Plasticity due to deprivation

Much of what we have learned about the plasticity of the auditory system due to deprivation comes from animal studies. Recall that the cochlea and brainstem are organized tonotopically and that this organization is also present in auditory cortex. In animal studies of neural plasticity after deprivation, specific areas within the cochlea or in the brainstem are lesioned so that a range of frequencies will no longer be encoded and transmitted to auditory cortex. Following lesioning, the organization of auditory cortex is studied to determine if there are frequency specific changes, reflecting neural plasticity. Irvine and colleagues have conducted many studies using this general approach and reported evidence that the cortical frequency maps do indeed undergo changes following the lesioning (Rajan *et al*., 1993). We cannot ethically lesion human cochlea or brainstems and so our studies of plasticity following deprivation in humans must be accomplished in a non-invasive manner. While these studies are still in the early stages, there is evidence that adults with sudden onset high frequency hearing loss have some changes in neural population response in auditory cortex, implying that cortical organizational changes occur following hearing loss in humans in a manner similar to findings in animal studies (Dietrich *et al*., 2001). However, these adults had sudden onset hearing loss and far less is known about slow onset hearing loss that may occur over many years or about more subtle forms of hearing loss.

What about children who are born with partial or complete deafness? When they are fitted with hearing aids or implanted with cochlear implants, will they develop normal hearing? Eggermont and colleagues have investigated the responses in auditory cortex in typically developing children and children with hearing loss who had cochlear implants (Ponton *et al*., 1996a, b). The implanted children showed some maturational lag compared to the controls. However, following implantation their auditory system continued to mature in a typical fashion, showing evidence for plasticity in the implanted children. These results are heartening in that they show that auditory cortex may develop in a typical way even if there is deprivation early in life.

6.2 Plasticity due to learning

Our auditory system is constantly exposed to novel sensory inputs that must be decoded in order for us to interpret our listening environment. New voices, musical melodies, and environmental sounds are learned every day. What are the brain mechanisms for learning new sounds? How are these new sensory memories formed and where are they located in the brain? These questions have been the topic of years of investigation by scientists using animal models for understanding learning and plasticity in the auditory system. While some scientists hold that sensory-based memories are

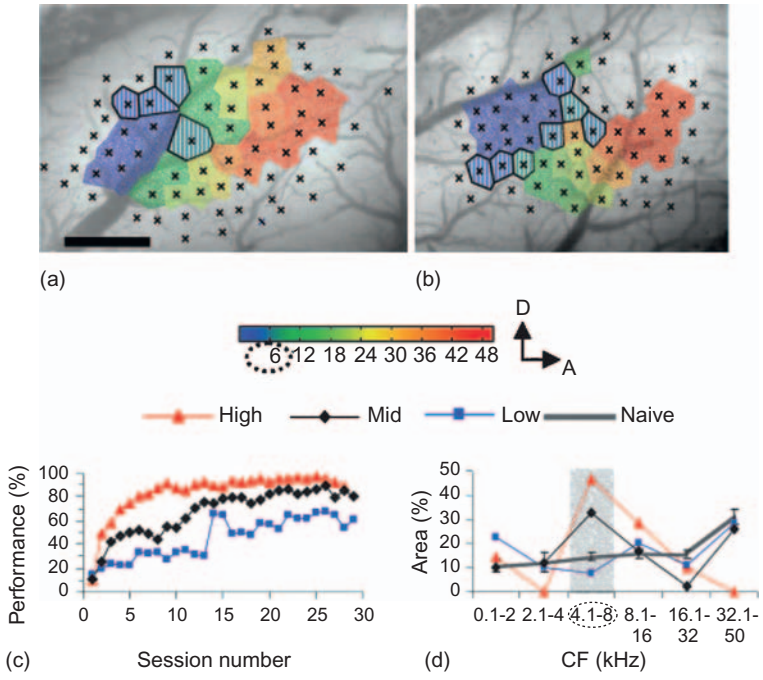

FIGURE 7.39 Examples of the effects of training on representational area. Organization of center frequencies (CFs) in A1 (primary auditory cortex) for a representative untrained naïve (a) and a trained experimental (b) rat. Each 'x' indicates an electrode penetration, with colored polygons indicating the estimated AI are representing the CF according to the color bar shown below the maps; D, dorsal, A, anterior. Cortical area representing CFs within the conditioned stimulus (CS) octave band, i.e. 4.1–8 kHz, is highlighted by outlined polygons and vertical hatching. (c) Learning curves for three animals showing low (blue squares), mid (black diamonds), and high (red triangles) levels of motivation level. (d) Corresponding distributions of relative representational area (percent of total A1 area) for each animal, together with mean naïve areas (gray line), are shown. Vertical bars on naïve area distribution indicate +/− SEM; dashed circle and light gray box highlight the CS bin. *Source*: Adapted from Rutkowski and Weinberger, 2005.

formed and stored in central memory systems, others suggest that these sensory-specific memories are formed and stored within the sensory area in which they were learned. For example, Weinberger and colleagues (see Rutkowski and Weinberger, 2005, for a recent review) have developed a model for auditory learning that holds that the changes in neural tuning for new and relevant sounds happen almost immediately, within a few trials of training, and occur in primary auditory (A1) cortex. According to this view, the neural tuning of neurons in A1 changes to reflect the features in sounds that are behaviorally relevant. Using classical conditioning experimental paradigms, Weinberger and colleagues presented tones paired with mild electrical shock. After conditioning, the representational maps of A1 reflected a reorganization, with more neural area devoted to encoding the frequency of the paired tone (Figure 7.39).

6.3 Plasticity due to expertise

Non-invasive behavioral studies show similar patterns for learning in humans in that learning changes occur fairly rapidly and are relatively long lasting. One aspect of learning that has intrigued scientists is whether highly trained musicians have a different kind of brain than unskilled individuals. Certainly, the musicians have spent more time and effort on musical training – does this change the way their auditory cortex is tuned? The work of Rupp and colleagues provides evidence that it does (Schneider *et al.*, 2002) (Figure 7.40).

The notion of brain changes due to situation-specific experiences such as hearing loss or deprivation, learning, and expertise is an intriguing one and there are many studies ongoing to investigate the correspondence between experience and mechanism, mind and brain.

7.0 AUDITORY AWARENESS AND IMAGERY

We can close our eyes and shut out visual images but we cannot close our ears to shut out auditory events. What is the effect on the auditory system? The auditory system is the last sensory system to fall asleep (or become unconscious with sedation) and the first to awaken. In this section, we highlight some recent studies of auditory awareness during less-than-conscious states, such as sleep or sedation. We also highlight studies of auditory activation for imagined-not-heard sounds. These aspects of auditory processing are in their infancy, however, brought about by the advent of neuroimaging techniques to measure brain responses that are not easily accessed using other techniques, and so much more work must be done before we can state definitively how auditory awareness and imagery are instantiated in the brain.

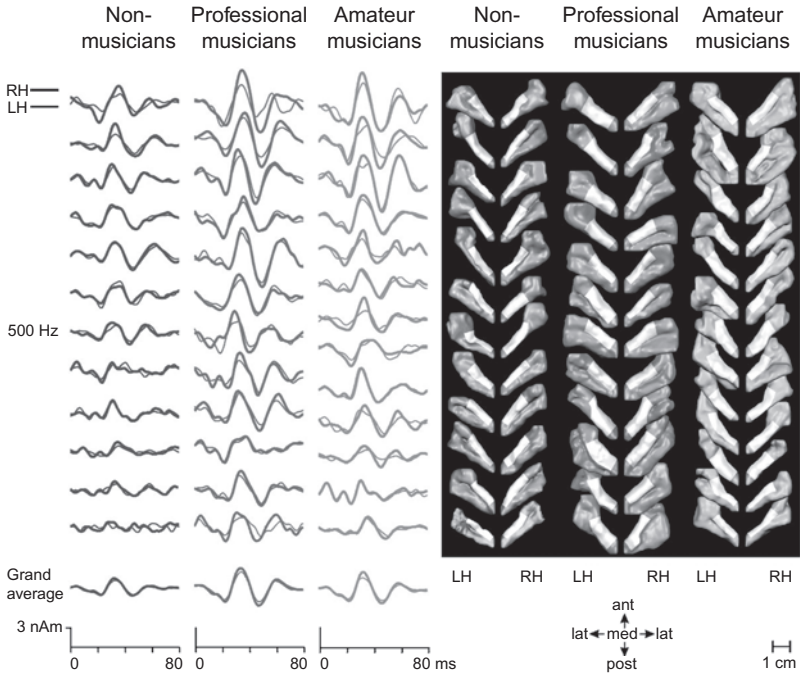

FIGURE 7.40 The neurophysiological and anatomical data show a large increase in professional musicians and a smaller increase in amateur musicians. *Left*: Dipole strength of the primary cortical response at 500 Hz. Sources in the right (thick lines) and left (thin lines) hemispheres are superimposed. *Right*: Highlighted areas show the Heschl's gyrus for each subject, aligned in the same order as the primary evoked responses. *Source*: Adapted from Schneider *et al.*, 2002.

7.1 Auditory awareness during sleep and sedation

Think about the best way to wake up a sleepy friend – call his name! A neuroimaging study investigated brain responses in sleep and in wakefulness in two conditions: neutral, where the sound was a simple beep, and significant: where the sound was the subject's own name (Portas *et al.*, 2000). Two main results of that study were that beeps and names activated auditory cortex both when the subject was awake and when the subject was sleeping, indicating that auditory cortex processes sounds even during sleep (Figure 7.41). A second key finding was that auditory cortex response for the neutral tone versus the subject's name did not differ during sleep, indicating that auditory processing during sleep encodes the presence of sounds but did not differentiate between these very different sounds. Brain activation patterns for names versus tones did differ, however, in middle temporal gyrus and frontal lobe regions. There were also areas in the amgydala that were more active during the presentation of the subject's own name during sleep than when awake. Do these brain areas represent a circuit in the brain that alerts us to wake us up when we hear our own name? More investigations are needed to support this theory, but, these findings provide intriguing evidence for how the auditory system 'wakes itself up'.

A related finding was recently reported by Zatorre and colleagues (Plourde *et al.*, 2006) in a study investigating the effects of anesthesia on surgical patients. Many recent studies have investigated the level of auditory awareness in surgical patients who are anesthetized, with the primary motivation of ensuring that anesthetized patients do not hear sounds in the operating room that may be upsetting to them. Results of the study by Zatorre and colleagues are similar to those reported by Portas and colleagues: auditory cortex was activated by simple and complex sounds during anesthesia and response patterns did not differ for speech versus non-speech sounds (Figure 7.42).

The authors interpreted these findings to indicate that while auditory cortex responds to the presence of sounds, even during sedation, the response is non-specific. This is a similar finding to the results for beeps and names during sleep and wakefulness. However, in the anesthesia study, the authors suggested that their findings of no differences across types of sounds meant that complex (semantic, emotional) processes engaged during conscious states were not activated during sedation. Which study is right? More investigations with similar stimuli and experimental designs must be conducted in order to determine if there are brain areas that are active during sleep or anesthesia and that might reflect the brain's monitoring of auditory events.

7.2 Auditory imagery

'Sounds not heard' are playing in our heads all day. Some sounds are uncalled for; they just seem to

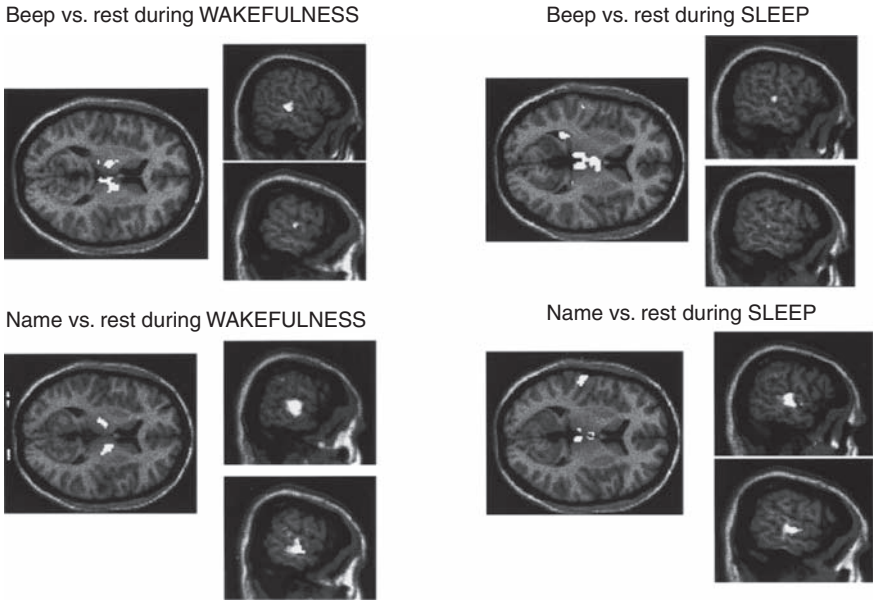

FIGURE 7.41 *Upper panel*: Brain areas active for beep versus rest during recorded during wakefulness and sleep. *Lower panel*: Brain areas for name versus rest recorded during wakefulness and sleep. *Source*: Adapted from Portas *et al.*, 2000.

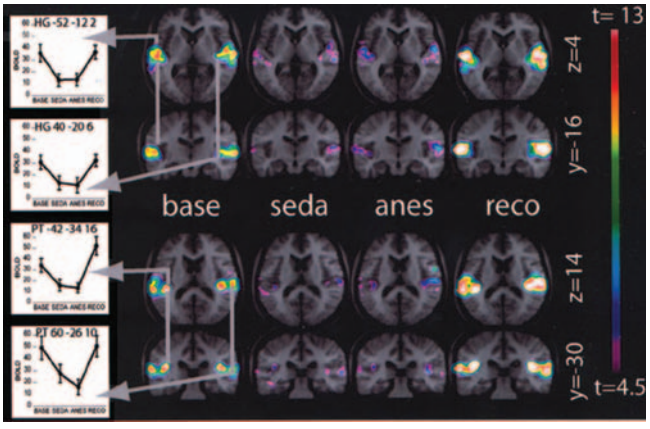

FIGURE 7.42 Group average responses for all sounds-silence. Activation maps overlaid over average anatomical images. The right side of the images corresponds to the right hemisphere. Line diagrams show the mean signal amplitude (difference in effect size between the two conditions, i.e. sound versus silence). *Source*: Adapted from Plourde *et al.*, 2006.

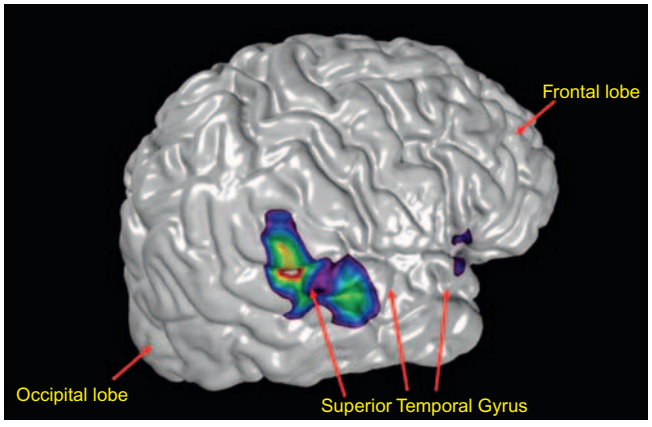

FIGURE 7.43 Illustration of brain areas active for imagined sounds. *Source*: Adapted from Zatorre and Halpern, 2005.

happen: a melody that spins around in your head, your inner voice talking to yourself. Other sounds not heard aloud are planned: practicing lines for a school play or rehearsing a phone number before dialing. Where are these sounds processed in the brain? We are aware that we actually seem to 'hear' these inner sounds. Does that mean that auditory cortex is activated when they are playing despite the fact that there is no actual sound? Halpern and colleagues (Zatorre & Halpern, 2005) have investigated this question using neuroimaging techniques to measure brain activation for imagined sounds versus heard sounds. Results (shown in Figure 7.43) show that non-primary auditory cortex is indeed active during imagined – and not heard – sounds.

A related finding was reported by Jancke and colleagues (Bunzeck *et al.*, 2005). These investigators wanted to study auditory imagery for environmental

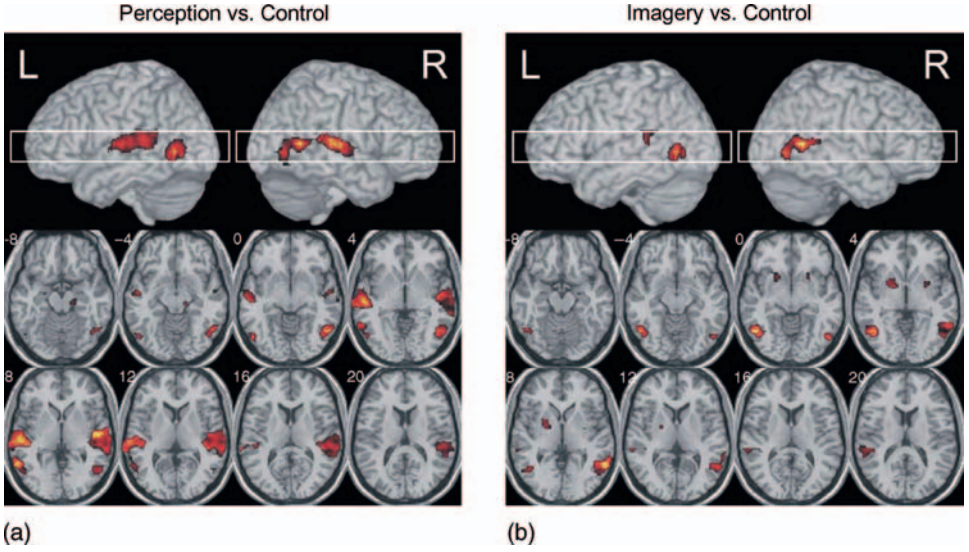

FIGURE 7.44 fMRI study of perceived sounds versus imagined sounds. The sounds used in this study were neither language nor music, in order to determine the localization of imagined non-linguistic or musical sounds. Primary auditory cortex was active during the perception phase of the experiment but not during the imagery phase. *Source*: Adapted from Bunzeck *et al.*, 2005.

sounds. Using fMRI, they recorded neural responses to subjects perceiving sounds and imagining those sounds. Results are presented in Figure 7.44: primary and secondary auditory cortex in both hemispheres is active when perceiving sounds (left panel), while secondary (and not primary) auditory cortex is active when imagining those same sounds (right panel).

These findings provide compelling evidence that imagined sounds activate similar neural regions in auditory cortex that are activated when sounds are heard. Recall the learning data from Weinberger and colleagues showing that sound-based memory and learning occurred in auditory cortex. The findings presented here, while representing only a small proportion of the on going investigation of auditory imagery, indicate that similar processes occur in humans as well, with imagining and perceiving sounds sharing neural territory.

8.0 SUMMARY

In this chapter, we presented an overview of the complex auditory system, from hearing basics to music perception to auditory imagery. The advent of neuroimaging techniques has provided a wealth of new data for understanding the cortical auditory system and how it interfaces with other cortical regions. While we have made major inroads on understanding the puzzle of auditory perception, there is still much work to be done. For example, teasing apart neural systems that underlie music and speech perception is still in the early phases. There are many other key questions that are being addressed in the field of auditory brain science. For example, what are the differing roles of the left and right hemispheres in speech and music perception?

There is fruitful work in the investigations of processing streams in the auditory system and in the brain. And while the work in non-human primates has informed us greatly about the existence of 'where' and 'what' processing streams, these streams may be established differently for humans due to the unique and important roles of speech and music perception in the evolution and development of the human brain. The next time an uncalled melody plays inside your head, consider the areas that might be activated in your brain as you 'hear' your silent song!

9.0 CHAPTER REVIEW

9.1 Study questions

1. What are the basic physical features and psychological aspects of sound?
2. What are the main parts of the auditory system and what are their roles in perception?
3. Briefly describe some differences between the 'what' and 'where' processing streams.
4. What are the basic units of analysis for speech perception?
5. What have new brain imaging techniques provided us in terms of investigating auditory function?

9.2 Drawing exercise

We highly recommend drawing and coloring to help you remember the physical layout of the brain.

1. Top panel of Figure 7.45: identify auditory cortical areas that are visible on the lateral aspect of the brain.
2. Bottom panel of Figure 7.45: identify the auditory cortical regions denoted by blue, pink, and brown shading.

9.3 Exploring more

Suggested reading and web sources:

Blumstein, S. E. (1997). A perspective on the neurobiology of language. *Brain and Language*, *60*(3), 335–346.

Hickok, G., & Poeppel, D. (2004). Dorsal and ventral streams: A framework for understanding aspects of the functional anatomy for language. *Cognition*, *92*, 67–99.

Moore, B. C. (2002). Psychoacoustics of normal and impaired hearing. *British Medical Bulletin*, *63*, 121–134.

Peretz, I., & Zatorre, R. J. (2005). Brain organization for music processing. *Annual Review of Psychology*, *56*, 89–114.

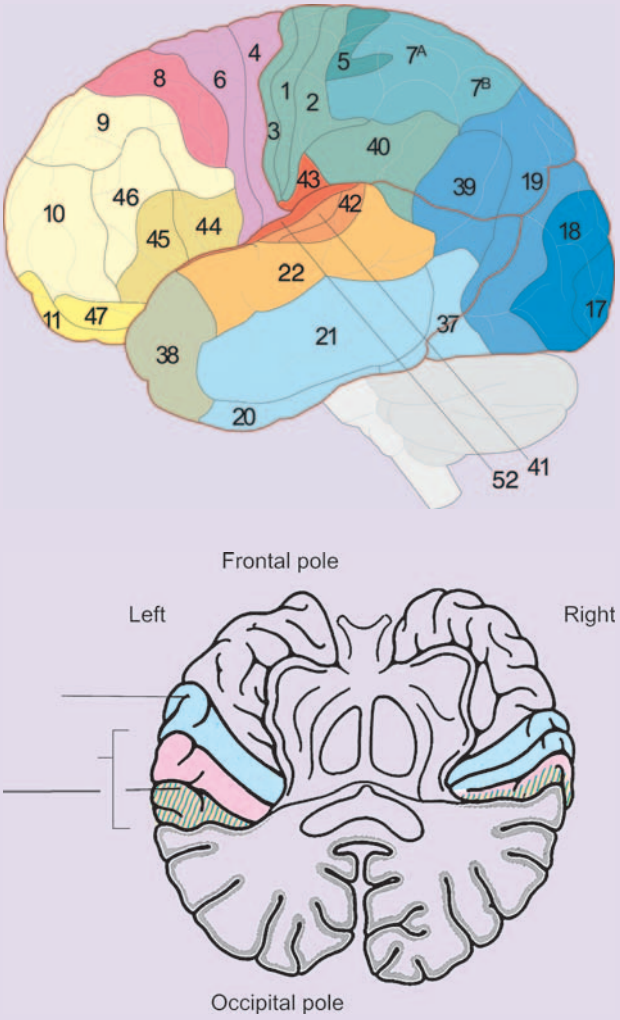

FIGURE 7.45 An axial (horizontal) slice of the brain showing the anatomy of auditory cortex in left and right hemispheres.

NIH website on the auditory cortex <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid = neurosci.section.919/>.

NIH website for searching the literature on auditory processes Entrez Pubmed – < http://www.ncbi.nlm.nih.gov/entrez/>.

You can enter names of scientists mentioned in this chapter into a search engine like Google. Many have laboratory websites that are interesting to explore. <http://www.google.com/>.

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Millions of items … are present to my senses which never properly enter into my experience. Why? Because they have no interest for me. My experience is what I agree to attend to …. Each of us literally chooses, by his ways of attending to things, what sort of a universe he shall appear to himself to inhabit.

William James (1890), The Principles of Psychology

The central scene of a famous painting by Diego Velazquez (1599–1660) called Las Meninas, or The Maids of Honor, who are the Royal companions of the Infanta (the little girl at the center) the Princess of Spain and the daughter of King Philip IV and his Queen – who are shown in the shadowy painting at the back of the room. It is widely believed to be a contemplation of self-consciousness, one of the topics of this chapter. Notice that almost everyone in this painting seems to be paying attention to themselves, or to a mirror image of themselves, starting with Velazquez himself (on the left) who is looking into a large mirrror in order to paint the entire scene. We, the viewers, are therefore part of the scene, because it is painted from the viewpoint of the audience. The Infanta herself seems to be wondering if she is looking pretty. Children develop social self-consciousness around the age of four. It is a profoundly important aspect of the human mind-brain and of our social existence. (*Source*: Wikimedia. The original painting hangs in the Prado Museum in Madrid.)

CHAPTER

8

Consciousness and attention

OUTLINE

1.0 INTRODUCTION

We wake up each morning to an ongoing stream of conscious events. As we open our eyes, the visual world comes alive again. A flow of coherent inner speech also begins as we wake up – we start to talk to ourselves. Conscious contents begin to be encoded as episodic memories, so that we can learn and recall experiences (see Chapter 9). By comparison to the waking state, we generally have poor recall for sleep events, even for dreams that occurred just before awakening. Yet we dream for 90 to 120 minutes each night. Therefore, most dreams will never be recalled.

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

As we come to consciousness each morning we remember our most important current goals. That means we can exercise voluntary attention over the information that will come to our consciousness. As William James wrote (above), 'My experience is what I agree to attend to.… Each of us literally chooses, by his ways of attending to things, what sort of a universe he shall appear to himself to inhabit'. James does not explain spontaneous attention – the things we pay attention to even though they are not voluntarily brought to mind. But he explains how over time, the things we choose to pay attention to come to dominate our conscious waking periods.

As we awaken we can control our skeletal muscles again – unlike during the near-paralysis of sleep – so that we can stand up, scan the world, go hunting and gathering, and talk with each other. Each of those capacities recruits a different network of brain events that can only be learned, mobilized, and controlled in the waking state. In the waking state we have a vast repertoire of abilities that are not available in other states.

Our functional diagram (Figure 8.1) shows the concept of 'attention' as an arrow going *from* attentional control regions *to* cognitive processes that are enhanced by attention. Voluntary attention is shown as an arrow running from the central executive (roughly, the frontal lobes) to brain activities that are enhanced by attention. Sensory cortex can also be enhanced by events that are not under voluntary control. If someone yells out loud, a large dog barks unexpectedly from a few feet away, or a truck looms into your field of vision, attention will be stimulus driven. Many biologically significant events trigger attention 'bottom up', such as the smell of food when you are hungry. We spontaneously select personally significant stimuli as well, like the sounds of our own names. We can symbolize stimulus-driven attention with an arrow coming from the sensory boxes of the diagram to suggest that some stimuli are inherently attention-capturing.

The sensory regions of the posterior cortex are especially sensitive to attentional enhancement. However, the motor cortex, Broca's area, and semantic memories can also be selectively attended.

If we take conscious experiences in many cases to be the results of selective attention, that can also be readily expressed in the diagram. Although there is

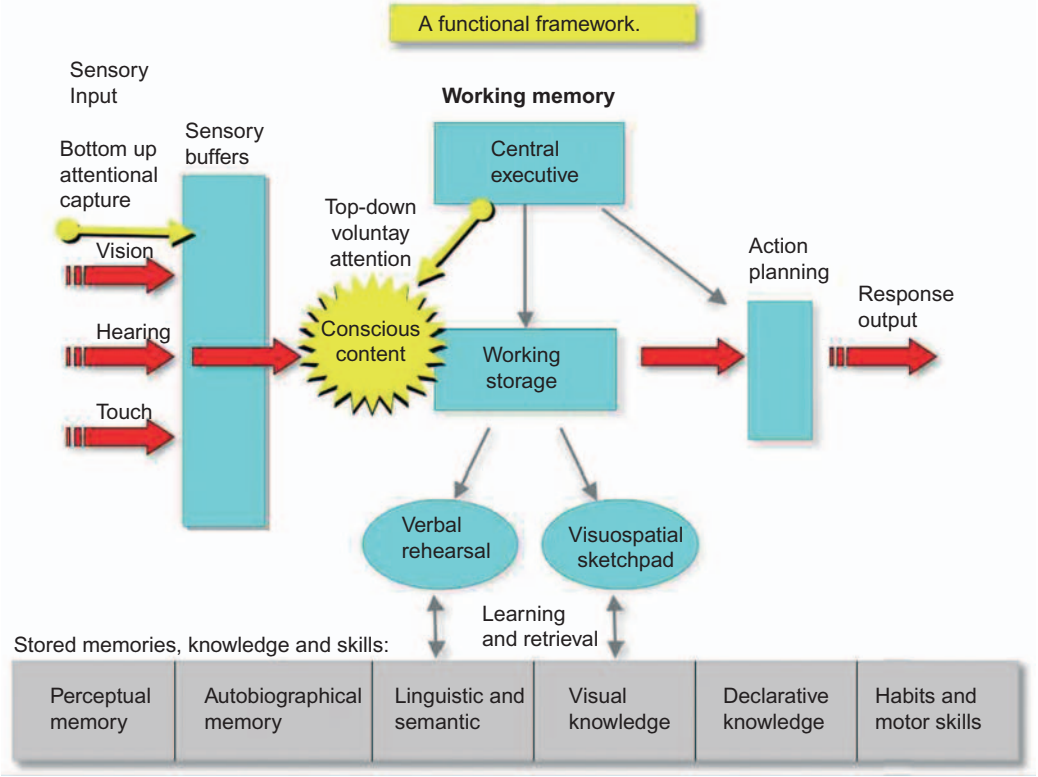

FIGURE 8.1 A functional framework for attention and conscious events. How consciousness and attention appear in the functional framework. Notice that attention can be under voluntary control by the central executive, since people can be asked to pay attention to a great variety of events. However, 'bottom up' attentional capture occurs when sensory events are intense, surprising, or significant enough to make us pay attention. Paying attention usually leads to specific conscious experiences. *Source:* Bernard J. Baars, 2009.

scientific debate as to whether *all* conscious experiences result from attentional selection, no one doubts that many of them do. Everyone who teaches has called the attention of the class to conscious events; it is how we begin any group meeting. Human and animal experiments do much the same thing. The link between attention and consciousness is an intimate one, a big part of our everyday psychology.

With careful studies we can separate the phenomena of attention and consciousness. To focus on conscious events 'as such', we typically study them experimentally *in contrast with* closely matched unconscious events, as we have seen in previous chapters (see Chapters 1, 3, 6, and 7). By contrast, experiments on attention typically ask subjects to select one of two alternative stimuli. 'Attention' is therefore concerned with the process of *selection* and consciousness, with reportable experiences themselves.

Some key questions for cognitive neuroscience are: What is distinctive about conscious events in the brain? What does it really mean for someone to be conscious? And how does the brain basis of attentional selection relate to our private, conscious experiences of the world?

FRONTIERS OF COGNITIVE NEUROSCIENCE

Consciousness

FIGURE 8.2 Christof Koch (left) is a well-known neurobiologist and researcher on the brain basis of consciousness. Koch worked for many years with Francis H.C. Crick (right), the Nobel Laureate and co-discoverer of DNA. Crick (1916–2004) devoted the last decades of his life to this topic and inspired other scientists to follow his lead.

How can we study consciousness? How can the relationship between subjective experiences, what philosophers refer to as *qualia* (the elements making up any one experience, whether it is the experience of seeing red, smelling cow dung, or being angry), and the brain be understood in an objective, quantitative, and empirical manner? Initially, there was a lot of resistance to the idea that one could study consciousness – whether in humans or in related animals, such as mice or monkeys – scientifically. 'Leave that work to retired Nobel laureates, philosophers, artists, literary people and the pyramid crowd'! was a common reaction. However, consciousness is a brute fact of nature. And it is, of course, the only way I – or anybody else – experience the universe and the only way I know that I exist. This is the genius behind the most famous deduction in Western thought, Descartes' *Je pense, donc je suis*. If we desire a scientific comprehensive view of the universe and everything in it, then consciousness must figure prominently in such a final description of everything there is. And over the past twenty years, we believe that we have made significant empirical progress in an inchoate science of consciousness. The approach that Francis Crick and I championed since our first paper on the topic in 1990, focusing for now on the *Neuronal Correlates of Consciousness*, the minimal neuronal conditions jointly necessary for any one specific conscious sensation, has borne ample fruits.

But when we have finally identified the elusive NCC, say for adult human visual perception, we will need to understand why this particular NCC does give rise to consciousness, and why not that one. And we will need to understand which nonhuman organisms are conscious. Although this is easy for closely related species, such as monkeys and mice, and probably for all mammals, this becomes much more tricky for cases that deviate from

this standard. Is a fetus conscious? What about one of the thousands of persistent vegetative state patients? A bee? A squid? To answer these and other questions in a definite manner we need a fundamental theory of consciousness. And the idiom of such a theory needs to be the mathematic of information theory, since information can express causal relationships among the many parts of any system independent of the substrate of this system, whether spiking neurons or silicon transistors.

In my eyes, the only plausible candidate for a fundamental theory of consciousness is the one by Giulio Tononi. Called the Integrated Theory of (ITT) Consciousness, it provides an exciting new way to study consciousness using a rigorous scientific approach (Tononi & Edelman, 1998; Balduzzi & Tononi, 2008; Tononi, 2008).

The ITT framework is built on the notion that consciousness is a consequence of systems that have both a large amount of differentiated information that is also highly integrated. In this context, integrated information means information that is accessible to the entire system as a whole. An iPhone, for example, has 16 Gbytes of storage space. This represents around 16 billion discrete distinct states. But they are not at all integrated. To the iPhone, each pixel in each image is identical to any other information, say, in its calendar. It does not realize, for example, that the various pictures of a young girl on my iPhone morphing into a self-assured woman is that of my daughter whose entry is in my phone book, and that she is related to the smiling confident man – her brother – in the next batch of images. For the current generation of iPhones (and other computers), all these pixels are equally meaningless (it does not even realize that images are inherently 2-D). ITT provides a precise way to calculate the size of the conscious repertoire, the state of consciousness as it were, using a number, measured in bit, called Φ.

Tononi's ITT provides a critical tool to ground consciousness in the natural world in a quantitative manner. According to Tononi, the amount of integrated information that you or I have in our brains corresponds to our repertoire of possible conscious states. Many fascinating questions are raised by such a theory. One is particularly fascinating from the point of designing machines (I'm not only a professor of biology but also one of engineering). Can artifacts made out of silicon, copper wire, and steel even be sentient? Can they too experience the world? ITT clearly argues yes, provided they have both highly differentiated as well as integrated information (Koch & Tononi, 2008).

For more information about the neurobiological aspects of consciousness, see my book, *The Quest for Consciousness: A Neurobiological Approach*. The research we carry out in my laboratory is described in detail at http://www.klab.caltech.edu/.

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Balduzzi, D., & Tononi, G. (June 2008). Integrated Information in Discrete Dynamical Systems: Motivation and Theoretical Framework. *PLoS Computational Biology*, *4*(6).
Tononi, G. (December 2008). Consciousness as Integrated Information: A Provisional Manifesto. *Biological Bulletin*, *215*(3), 216–242.
Koch, C., & Tononi, G. (June 2008). Can Machines Be Conscious? *IEEE Spectrum*, *45*(6), 55–59.
Christof Koch, PhD, Division of Biology, California Institute of Technology, Pasadena, CA, USA.

1.1 Waking cognition is consciously *mediated*

The waking state supports an endless set of adaptive functions. During waking consciousness we learn new actions, feelings, words, ideas, skills, goals, and even new kinds of sensory events, like a new way of understanding music or visual art; each one involves distinctive patterns of brain activities. The set of waking state functions is therefore an open set, one that can keep expanding as long as our brain is alive. The most basic ones are discussed throughout this book: vision, audition, memory, emotions, executive control, social cognition, and so on.

Each waking task has both conscious and unconscious components. For example, the lower ventral stream of vision yields reportable conscious object representations, like visual coffee cups or a kitchen chair. The upper dorsal stream of the visual brain represents body space and controls actions like manual reaching, but its contents are not reportable as conscious (Milner and Goodale, 2007). Yet both the dorsal and ventral streams require the *state* of waking consciousness to work. Almost all cognitive tasks we know take place during the waking state and have both conscious (reportable) and unconscious (nonreportable) components.

Most cognitive tasks we know are therefore consciously *mediated*. Working memory, for example, has both conscious and unconscious components. If you rehearse seven numbers you will notice that some are conscious at any moment, but others are not. The instructions to rehearse and remember are obviously conscious and so is the set of items as you see or hear them. But we are not aware of the nonrehearsed items at any moment, of the important role of the basal ganglia in controlling inner speech, or of the automatic (habitual) components of any task. There are no completely conscious cognitive tasks, as far as we know, and there

may be no completely unconscious ones (Baars and Franklin, 2003; Prof. Stan Franklin has suggested the term 'consciously mediated' for cognitive tasks that have a conscious but are otherwise unconscious).

The basal ganglia and cerebellum are very large brain structures that are believed to function without supporting moment-to-moment conscious contents, even in the waking state. The cerebellum can actually be lesioned on both sides, and people and animals will continue to behave much as before but without the ability to control fine motor movements. In humans those structures have many other cognitive roles but without leading directly to conscious contents.

What can we do completely unconsciously? We still do not know the answer, because it is difficult to do careful studies on sleepwalking, sleep movement disorders, epileptic 'automatic behaviors', and other 'zombie states' (Crick and Koch, 2003). There are many reports about automatic behaviors from individuals with sleep disorders and epilepsy. To verify those reports we need brain recordings that are difficult to obtain in freely moving people. It is also possible that epileptic behavioral automatisms, for example, reflect momentary conscious 'flashes' that are known to exist (Kranczioch *et al.*, 2006). It is therefore hard to test whether there are complex but entirely unconscious behaviors, in part because we simply do not know the distinctive brain correlates of consciousness as yet (but see Gaillard *et al.*, 2009; Revonsuo, 2008). We do not know yet what difference enables consciousness of the ventral but not the dorsal stream of the visual cortex. There are ongoing efforts to make progress on those questions, however (Laureys and Tononi, 2008).

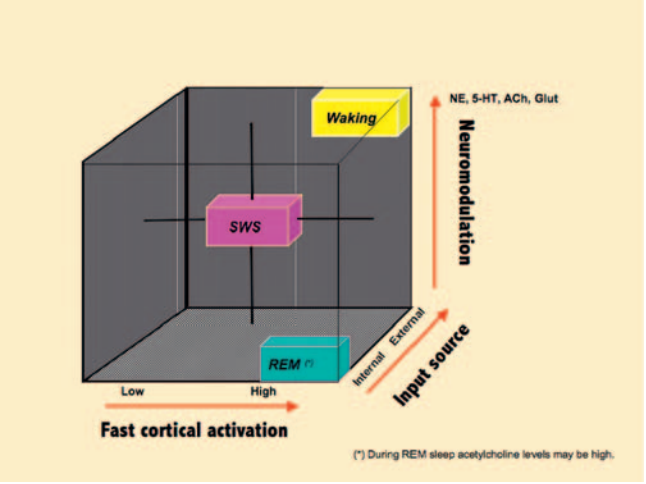

FIGURE 8.3 Three dimensions of waking, sleep, and dreaming. Many state-related phenomena can be described in three dimensions (Hobson *et al.*, 2000; Giocomo and Hasselmo, 2007). 'Fast cortical activation' refers to widespread, fast, irregular, and low-amplitude activity in the EEG. 'Input sources' are either internal, as in dreaming, or external, as in waking. 'Neuromodulation' refers to four widespread neurochemicals that are turned on and off by basal brain nuclei. They are acetylcholine (ACh), norepinephrine (NE), serotonin (5-HT), and glutamate (Glut). These molecules play vital roles in perception, action control, and learning. SWS refers to slow-wave sleep, marked by delta waves in the raw EEG. SWS has the highest arousal threshold of the circadian cycle. *Source*: Adapted from Hobson, 2000.

1.2 The need for timely waking, sleep, and dreaming

Chronically sleep-deprived rats die after only three weeks. We know, therefore, that sleep is needed for survival in mammals, but its exact functions are still unclear. Sleeping animals are more vulnerable to predators. Our nightly eight hours of loss of consciousness of our environment must therefore have some compensatory advantages. We do know that sleep and dreaming seem to enable memory consolidation, converting new and unstable memories into lasting ones. Sleep, dreaming, and waking are complex states, with long evolutionary histories. Like other major adaptations they have probably gathered many biological functions. A large number of genes are known to be expressed in sleep, and many genes change their expression due to sleep deprivation. Scores of biological parameters seem to be turned off and on by sleep and its loss.

Sleep duration appears to be under homeostatic control, since we tend to make up for lost sleep by sleeping longer. Sleep-deprived individuals show 'microsleeps', moments of 'dropping off', that can seriously interfere with actions like driving. You can observe moments of dropping off just by studying late into the night. When your brain rapidly switches from waking to sleep, state-modulating brain and spinal chemicals switch quite quickly (Figure 8.3). In a second or two, your neck muscles can lose tone, and your head will tend to drop forward. Spinal and cranial motor nerves switch to inhibition, and it's time to get some rest. We have some cortical control over staying awake, but eventually the biological clock will win out.

Surprisingly, a single night of sleep deprivation can also improve depression, even when other treatments have failed. Staying up for one night therefore has been suggested as a safe, inexpensive, and effective treatment for depression. But *chronic* sleep deprivation is stressful and degrades normal conscious functioning.

The sleep-waking cycle is controlled by a biological clock, triggered in part by daylight onset and offset. A small group of retinal light receptors detect light

onset, signaling the suprachiasmatic nucleus, the pineal gland, hypothalamus, and deep brain nuclei, in order to release state-specific molecules. The major neuromodulators have state-specific actions (Figure 8.3). Changes in serotonin, norepinephrine and acetylcholine have been well described to trigger changes in the major brain states (see Chapter 16).

1.3 Global rhythms of circadian states

At the moment of awakening from sleep, billions of neurons change from the slow, unified 'buzz-pause' of slow-wave sleep to much more differentiated and task-specific signaling. The difference between sleep and waking is not just behavioral and subjective. Figure 8.4 shows the basic patterns we find in the 'raw' (unanalyzed) EEG in the three basic states.

Although scalp-recorded EEG is very useful, it is relatively crude, since it shows the additive results of billions of fast electrical signals from huge cell populations, filtered through dense layers of tissue and bone. Much effort has been devoted to finding out the brain basis of these states by using depth electrodes and brain imaging. Much of what we know about the thalamocortical system comes from studies in other mammals and in human medical patients. All mammals share the basic thalamocortical system. The raw (unanalyzed) EEG seems relatively crude, but even surface EEG shows fundamentally important information about sleep, waking, and some disorders like epilepsy.

Figure 8.4 shows the difference in surface EEG between waking, sleep, and REM dreaming. Each EEG state also has typical subjective experiences. Surprisingly, slow-wave sleep shows some mental activity as well; however, deep sleep is statistically less likely to yield reports of mental activity. Deep sleep is the least conscious state of the normal daily cycle, as measured by behavioral arousability – the likelihood that an animal will sit up, orient its receptors, and show waking EEG in response to a stimulus.

The standard surface EEG is generated by near-to-the-scalp branches of cortical neurons; these are typically the dendrites at the apex (top) of pyramidal cells – pyramid-shaped neurons with long axons that point downward from the scalp. Their long axons connect to other parts of the cortex or the thalamus. Pyramidal cells are excitatory, using glutamate as their major neurotransmitter, but they are surrounded by small inhibitory interneurons that use GABA as their neurotransmitter. Excitatory and inhibitory neurons work together in the same local patch of cortex. Cortical neurons are stacked in minicolumns of six layers (see Chapter 5), which interact constantly with thalamic cells, so that in the surface EEG we are seeing the massive summed oscillations of the thalamocortical system as a whole. That system is the brain basis for states of consciousness.

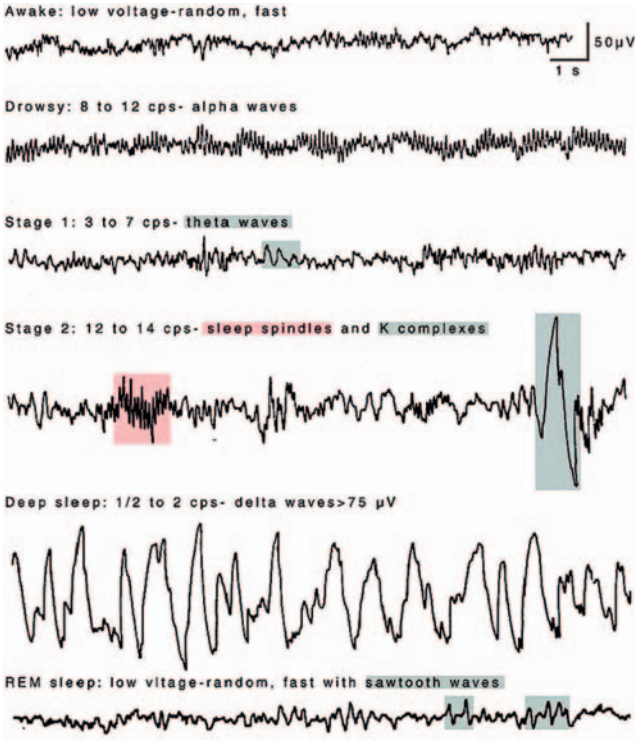

FIGURE 8.4 Surface EEG of the major states. The brain generates an electromagnetic field that can be recorded on the scalp. Each trace represents field oscillations resulting from billions of small neuronal voltages near the surface of the cortex, filtered through layers of tissue. The raw EEG reflects a complex mix of many different waves, but each state shows dominant waveforms that are quite distinctive. Notice the similarity between waking EEG (top) and REM dreaming (bottom). Judging by brain electrical activity, REM dreaming looks like a conscious state – which is indeed what we experience during dreams. As we get drowsy and go into deeper stages of sleep (Stages 1–4), sleep spindles, K complexes, and slow delta waves appear. (Delta is defined as less than 3 Hz.) More recently, slow oscillations have been studied, going down to .01 Hz. In deep sleep, mainly delta waves are visible, reflecting the simultaneous 'buzz' and 'pause' of billions of neurons firing and pausing together. However, it is now known that very slow oscillations occur even during the waking state. cps = cycles per second; *Source*: Squire, 2008.

It has been difficult to get 'clean' brain signals using scalp EEG, although there has been marked progress over the years. As you know from Chapter 4, MEG allows for better spatial localization than surface EEG, though it picks up slightly different sources. Local field potentials can be recorded throughout the brain with depth electrodes. Nevertheless, EEG is the most widely used brain recording technique because it

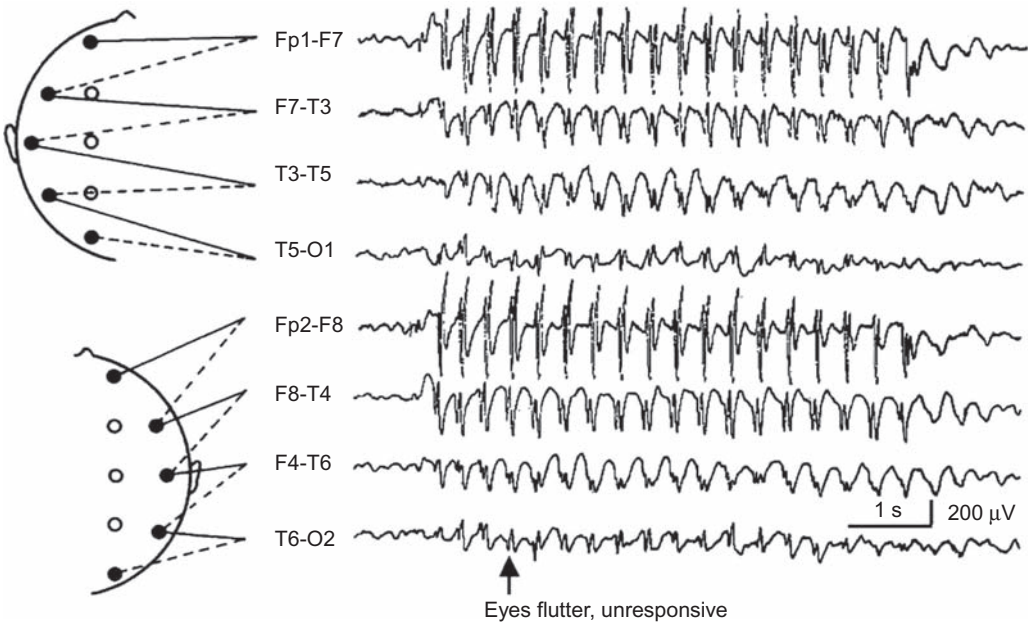

FIGURE 8.5 Slow hypersynchrony in epileptic loss of consciousness. The surface EEG of a 7-year-old girl during an epileptic seizure with loss of consciousness. Epileptic loss of consciousness shows slow, hypersynchronized global EEG similar to deep sleep but characteristically more jagged. Other unconscious states, like coma and general anesthesia, also show slow, high-voltage, and synchronized waves spreading over the cortex, suggesting that synchrony by itself is not the marker of consciousness. *Source*: Blemenfled, 2005.

is relatively inexpensive, picks up vitally important medical phenomena (like epilepsy and sleep disorders), and careful mathematical analysis helps to 'clean up' the signal.

EEG resembles the kind of information space aliens might pick up from radio signals coming from the earth without understanding much human speech and with only a vague idea of what human beings might be saying. Nevertheless, there has been marked progress in understanding (e.g. Buzsaki, 2002). *Intracranial* recording is more accurate and produces much less noise, with the major drawback being its invasive nature. By far, the greatest number of depth recordings has been performed in other animals, but human intracranial EEG (iEEG) has now emerged as a major source of scientific evidence. iEEG goes back to the pioneer neurosurgeon Wilder Penfield some 50 years ago. The signal strength inside the brain is up to 1000 greater than on the scalp, and a wider range of frequencies can be recorded. In addition, iEEG is free of some experimental artifacts, such as the stray voltages coming from eye movements and scalp muscles. Human iEEG is performed only in medically justified circumstances, but it has added a great deal to our knowledge, as we will see.

Large brain regions outside of the thalamocortical system may have little direct effect on conscious states. For example, humans and animals with bilateral loss to the cerebellum show impaired fine motor control (finger and hand movements), but they retain waking consciousness of the world and of themselves. More recent research shows that the cerebellum does have cognitive functions, probably by interacting with cortex. Since the cerebellum contains about as many neurons as the cortex itself, this basic fact seems to show that consciousness is *not* just a result of a large number of neurons. Something else is required.

Edelman and Tononi (2000) have proposed that it is the *high interactivity* of the cortex and thalamus that enables it to support a vast repertoire of consciously mediated tasks and experiences. Figures 8.5 and 8.6 show the anatomical basis of that highly interactive and flexible capacity. By comparison, the cerebellum is much more compartmentalized, with separate groups of neurons that seem to operate in parallel with each other. The World Wide Web is a natural analogy for the thalamocortical system, since any computer on the Web can communicate with any other.

Deep sleep is the most unconscious state of the daily cycle, marked by slow, high-voltage waveforms, involving coordinated 'Up States' and 'Down States' among very large cell populations. The EEG of deep sleep has some striking similarities to epileptic loss of consciousness, as well as comatose conditions and general anesthesia (Figure 8.5).

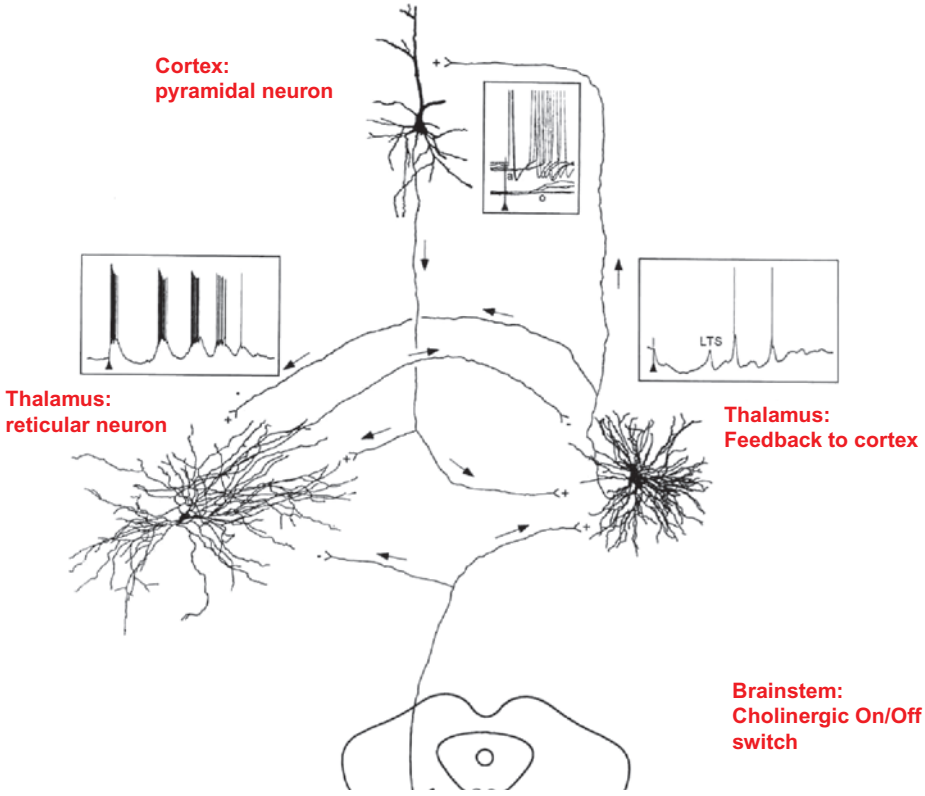

FIGURE 8.6 Three neurons in a thalamocortical loop. The basic rhythmic 'pump' of the brain. Waking, sleep, and dreaming are driven by thalamocortical oscillations. Thalamic nuclei interact closely with corresponding regions of cortex. This core brain is shared by other mammals and birds. *Source*: Adapted from Steriade, 2006.

Epilepsy may impair consciousness due to *hypersynchrony* of vast numbers of cortical and thalamic neurons. Figure 8.5 shows an EEG taken of an epileptic seizure in a 7-year-old girl during loss of consciousness (Blumenfeld, 2004). Notice the slow, high-amplitude waveforms, especially in her frontal lobes. These hypersynchronous waves often spread by 'recruiting' other parts of cortex. fMRI and PET show a drop in metabolic activity during seizures in the frontal and parietal lobes. Notice the rough similarity between natural slow-wave sleep (Figure 8.4) and loss of consciousness in epilepsy. Both of the EEGs show slow, synchronous activity in large parts of the thalamocortical core. However, the epileptic waves are much 'spikier' than deep sleep delta.[1]

There is an apparent paradox in global hypersynchrony in the EEG in unconscious states: On the one hand, synchronized brain rhythms allow widely separated regions of the brain to work together. On the other, the electrical storms of global hypersynchrony disrupt ordinary brain functions. It appears that normal survival activities cannot be carried out during global, hypersynchronous episodes.

One answer is that normal cognition requires *selective*, local synchrony among brain regions, and that the speed of working synchrony is faster than the ~1 Hz waves of deep sleep and epileptic seizures. Waking tasks use theta, alpha, beta, and gamma synchrony, covering a range of frequencies from about 4 to 200 Hz or even higher. Even 1000 Hz bursts have been observed during waking. Waking oscillations are highly patterned and *differentiated*, so that synchrony, desynchrony, and aperiodic 'one-shot' waveforms constantly appear and disappear (Tononi, 2004).

Waking consciousness resembles the flow of traffic in a busy city. At night, street traffic might dwindle to a few cars, but at rush hour, vehicles are constantly going from any location to any other. It is that ability to go anywhere, guided by local goals, that makes

[1] Coma patients, as well as patients under general anesthesia, may also show high and slow EEG. It seems that unconscious states commonly show high, slow, coordinated waves. In the worst coma cases, however, EEG will drop to very low voltages. Medical brain death is often defined as zero voltage in the EEG. However, recent studies show that conventional scalp EEG may not pick up residual brain activity in cases of coma. Medical researchers have therefore proposed a new diagnostic category, the 'Minimally Conscious State' (MCS), which may mimic true coma but still allows for conscious moments. A high percentage of patients who were previously diagnosed with irreversible coma are now believed to be in MCS, with intermittent conscious episodes (Laureys and Tononi, 2008).

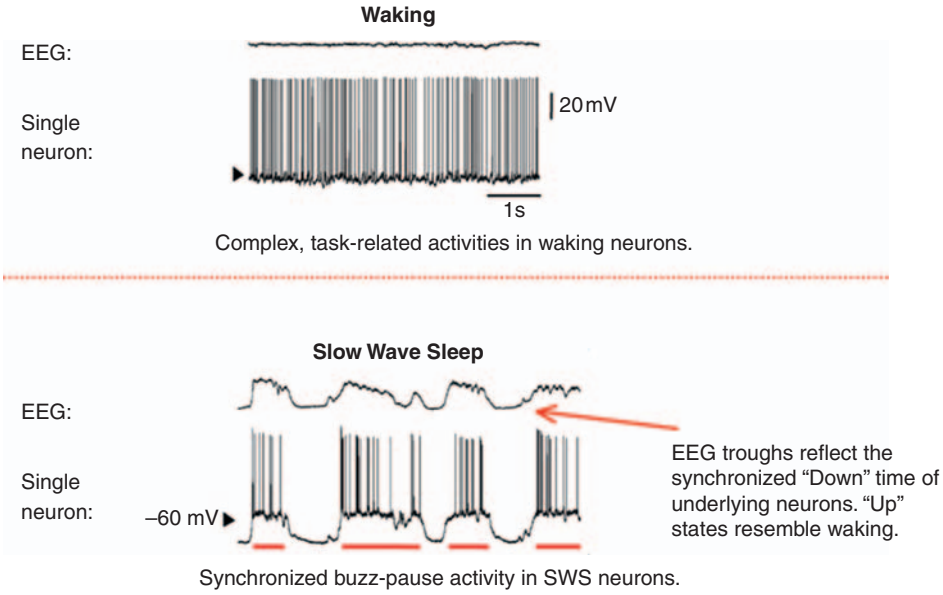

FIGURE 8.7 EEG and single-unit activity in waking and deep sleep. Conventional EEG measures the brain's electrical field over the scalp. Each EEG trace in the figure is a complex sum of underlying neuronal activity in the upper layer of cortex. Slow-wave sleep EEG reflects the simultaneous 'buzz' and 'pause' of billions of neurons, also called 'up' and 'down' states. Because waking-state neurons do not fire and pause synchronously, their voltages do not add up to large waves. The waking EEG looks small, irregular, and faster than slow-wave sleep. It is believed that waking (and REM dreaming) therefore involves more differentiated information processing in much the same way that a stadium full of talking people serves to process more information than the same people all chanting in unison. The unison chanting is largely redundant (you can predict the crowd chants from just one person) so the information content is lower (see Section 6.2). Adapted from Steriade, 2006.

vehicles useful. Similarly, waking tasks serve a huge variety of functions with great flexibility. In contrast, in slow EEG hypersynchrony all the traffic lights seem to turn green for a few seconds, then red, then green again, over and over again. The flow of traffic therefore is forced to screech to a halt in unison, then start again, stop again, and so on. The normal, flexible flow of brain signaling is constantly disrupted.

1.4 States of consciousness have characteristic thalamocortical activity

Figure 8.6 shows the basic unit of the thalamocortical system, consisting of three connected neurons in cortex, the thalamus, and the reticular nucleus of the thalamus. The cortical neuron in the figure is a pyramidal cell, named after the pyramid-shaped body of the cell. These are the long-distance excitatory neurons of the cortex, often surrounded by smaller cells. Keep in mind that the thalamus is considered to be the 'gateway to cortex' and that most thalamic nuclei have a corresponding region of cortex with which they interact. Some thalamic nuclei, like the LGN (see Chapter 6), involve relay neurons from sensory to cortical regions. Others are *corticocortical*, allowing attentional systems of the parietal and frontal lobe to enhance sensory processing in posterior cortex (via the pulvinar and mediodorsal nuclei of the thalamus).

Together the neurons in Figure 8.6 form a circuit that determines the major states of the circadian cycle. A fourth cell deep in the brain can turn this circuit on and off by squirting neuromodulating chemicals throughout large parts of the forebrain. There are many millions of such circuits, yet the basic simplicity of this thalamocortical loop is striking (Figure 8.8).

We can think of such a loop as an oscillatory circuit consisting of three oscillating units. Like the children on two playground swings that are suspended from a single crossbar (see Chapter 3), each unit can be treated as an oscillator. But the swing set as a whole is also an oscillating system. Single neurons are fast-charging and fast-discharging electrical wave generators. Circuits of neurons oscillate in more complex patterns. The thalamocortical loop of Figure 8.6 can be thought of as a fundamental rhythmic pump of the brain, operating differently in the global brain states of waking, slow-wave sleep, and REM dreaming.

Figure 8.7 shows how during waking, millions of individual neurons are firing largely independently of each other. Even though populations of neurons fire in

synchrony during the waking state, their interactions are relatively fast (perhaps 4–200 Hz) and local; fast synchrony appears to be task related, and it alters as mental activities proceed. As a result, neuronal firing in waking does not add up to large, global waveforms, unlike SWS (Figure 8.7, bottom). In SWS, massive numbers of neurons in the thalamocortical system fire simultaneous bursts and pauses about every other second, adding up to slow EEG waves in the global EEG. Such delta waves are conventionally thought to range from 0.5 to 3 Hz, but they have recently been found to extend into the slow oscillation range (0.01–0.5 Hz).

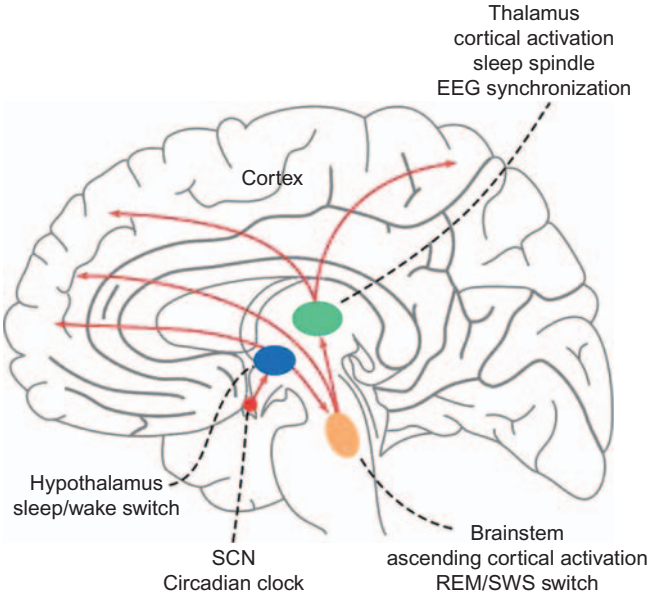

FIGURE 8.8 Brain state switches. The light cycle is picked up by special retinal receptors, which connect to the SCN (suprachiasmatic nucleus, located just about the X-shaped 'chiasm' of the crossing optical nerves). SCN is part of a circadian circuit that runs many brain and bodily functions. State changes are triggered by small brainstem and basal brain nuclei that send out neuromodulating fibers (see Chapter 16), which change the firing pattern of many billions of other neurons. The brainstem ascending cortical system participates in switching from slow-wave sleep (SWS) to REM. The hypothalamus, the endocrine center of the brain, is involved in the sleep-wake switch. The thalamus connects to all parts of the cortex and is a way station of almost all sensory nerves on their way to cortex. In SWS it generates sleep spindles (Figure 8.6). Together, these regions control the daily cycle of major brain states. They are the traffic control system for tens of billions of other neurons and trillions of synaptic connections. *Source*: Bacon *et al.*, 2007.

Another useful analogy is that SWS resembles a large football stadium in which all the fans chant and pause in unison every other second or so. When they shout together, the summed amplitude of the sound is very high. When they pause together, the total sound is very low. But when the audience members are just chatting with their neighbors, the sound is irregular, relatively low in amplitude, and much more complex. From this point of view, it is the waking state that carries the greatest amount of useful information (Tononi, 2004; see Section 7.0).

Current evidence based on these sources indicates a vital role for synchronized and interacting brain oscillations. They are believed to enable:

- Attention, perception, and conscious contents
- Learning, neural plasticity, and memory retrieval
- Long-range coordination between brain regions, including sensorimotor interaction

(Canolty *et al.*, 2006).

Brain waves often interact with each other, with slower rhythms tending to group faster ones. Interactions are often transient and related to specific tasks, as we will see. Both synchrony *and* desynchrony can play a role.

1.5 The thalamocortical core: massively interlinked and very active

It is easiest to think about the wiring of thalamus and cortex in terms of simple circuits, as described in

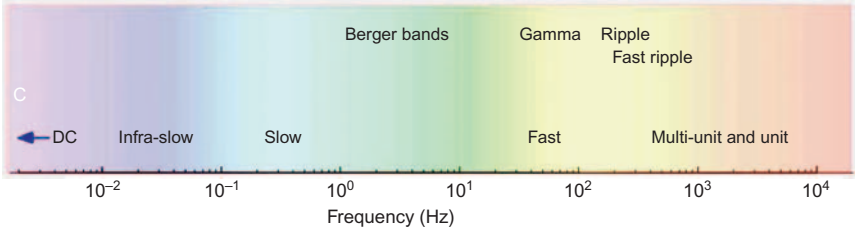

FIGURE 8.9 Brain rhythms range over several orders of magnitude. The wide range of functional brain oscillations. On the left, very slow activity appears as a rise and ebb of the voltage baseline. Very slow oscillations occur at <1 Hz, followed by theta, alpha, beta, and gamma. These labels are somewhat arbitrary. Very high-frequency events have been called 'ripples'. On the right side, single neurons and multiunit groupings show spikes up to 10 KHz. The range from 80 to 150 Hz is sometimes called the 'high gamma' range. *Source*: Bazhenov and Timofeev, 2006.

Figure 8.10 – just as it is easiest to think about automobile traffic in a large city in terms of single car trips from point A to point B. But it's also important to keep in mind the massive size of the whole metropolitan area – the thalamocortical system and its constant flow of traffic, with many 'signal trips' occurring at the same time. Izhikevich and coauthors have run large-scale simulation models of the system, which help us to understand how it works (Izhikevich *et al.*, 2004, 2008). The figures in this section show various aspects of the active core brain.

Most of the visible mass of the inner brain consists of white-covered neural fiber tracts, the myelinated neurons and their axons. These high-traffic highways have now been shown to follow the mathematics of 'small world networks', like the World Wide Web, which allows for the most efficient flow of signal traffic from any starting point in the brain to any destination (Achard *et al.*, 2007). Basically, a small-world network consists of high-traffic highways and hubs, along with numerous small streets and alleys for much more limited local traffic. Many networks in nature follow such an optimally efficient distribution of high-traffic and low-traffic links.

Figures 8.10A and 8.10B show the anatomical basis of the massive superhighway networks of the brain. The first figure shows the *thalamocortical* system in the left hemisphere, a vast number of two-way streets connecting cells in the left thalamus to those in left half of cortex. It is the thalamocortical system that we can see changing large-scale state activity in the major daily states of mind and brain – waking, sleeping, and REM dreams. These states are controlled by small nuclei in the basal brain, as pointed out earlier, which direct 'sprays' of neuromodulating axons to large regions of the brain including the cortex.

The second figure shows the *cortico-cortical* highway system, in which the signal traffic flows from one

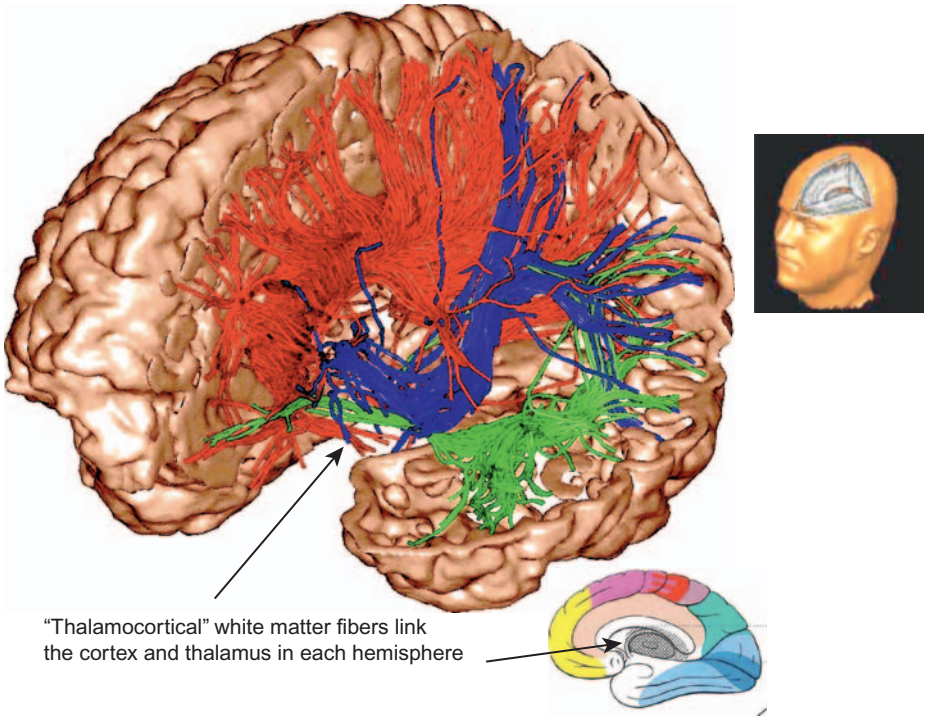

FIGURE 8.10A Thalamocortical fiber tracts. The massive size of axonal fiber tracts between the thalamus and the outer layers of cortex. Since axons coming from each cell body are wrapped in glial cells that are filled with lipid molecules, they appear white to the naked eye, and therefore were called the 'white matter' by traditional anatomists. These tracts are artificially colored in this computer-generated graphic, to show the different major pathways. All the fiber tracts seem to emerge from the left thalamus from the point of view that is shown here, but at least equal numbers of axons travel from cell bodies in cortex to the corresponding nucleus of the left thalamus. Traffic is always two-way or 'reentrant' in the thalamocortical system, a fundamental fact that requires explanation. Notice that there is no cross-hemisphere traffic in this image. The next figure shows equally massive cortico-cortical highways connecting the hemispheres laterally, mostly flowing across the corpus callosum. As Chapter 3 points out, it is possible to lose an entire hemisphere without losing consciousness, as long as the second hemisphere is spared along with the brainstem. *Source*: Izhikevich & Edelman, 2008.

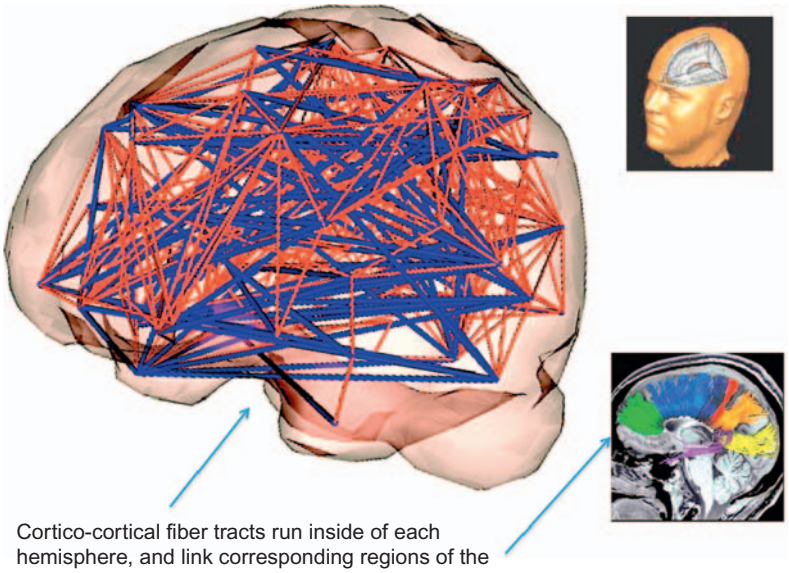

FIGURE 8.10B Corticocortical fiber tracts. The massive interconnectivity of the cortex. Like the World Wide Web, the cortex shows the mathematics of 'small-world connectivity', with highly traveled highways and traffic hubs that carry most of the signal traffic, along with numerous local and low-traffic streets and alleys. Most long-distance signals make use of the superhighways, the most efficient way for a vast and dense network to operate. Notice that the two hemispheres are extensively cross-connected, mostly across the white fiber bridge of the corpus callosum. *Source*: Human Brain Mapping Meeting, 2005.

point in cortex to another one. There are basically two kinds of cortico-cortical links, either within the same hemisphere, or from one hemisphere to the opposite one. The two hemispheres have an elegant parallelism in their connectivity, so that corresponding points from back to front of each hemisphere connect to the same point on the other side. Although there are important functional differences between the two halves of the cortex, such as in the production of language (which is usually supported by the left side), the most striking feature from an anatomical point of view is the great symmetry of the two hemispheres.

There are other major traffic systems in the brain, notably the *corticospinal* tracts, which carry information to and from the body via the spinal cord, and the cranial sensory and motor nerves. The visual and auditory systems discussed in previous chapters run through cranial nerves, whereas the somatosensory and somatomotor systems run through the spinal cord. However, we only need to think about the largest superhighways to get a good sense of the vastness of the metropolitan map of the brain and its constant traffic flow.

Keep in mind also that the thalamus is the major *input* hub for the cortex, and also the major cortex-to-cortex traffic hub, like a large airport that might serve both domestic and international traffic. However, the basal ganglia operate as a major *output hub*, for motor control and executive functions. The brain has multiple hubs, just as it has multiple superhighways. It helps to focus on the biggest ones because the basic principles are generally the same. But mammalian evolution has had 200 million years to grow the thalamus and cortex, on top of the more ancient structures like the brain stem, the spinal cord, and the olfactory brain. There is a great deal of redundancy in the system, just as there are alternative traffic routes in any large metropolitan area.

1.6 Maps and rhythms

Brain rhythms are much like timers and clocks. They support *temporal* coding in the brain. We also have discussed topographical *maps* in vision and other senses, which provide *spatial codes*. We can therefore observe both temporal and spatial coding of brain events, providing a very rich vocabulary of coding possibilities for the brain.

The retina can be thought of as a flat pixel map of the visual field (see Chapter 6). When light rays reflected from a coffee cup converge on the fovea – the densest spot of light receptors in the retina – that light pattern is believed to echo through multiple *visuotopic* maps in the visual brain. There are perhaps a dozen different visuotopic maps, each representing the visual field at a different level of analysis. We can think of those maps as echoing each other, beginning with the retina, then the visual thalamus and the primary projection area for vision, Area V1. Chapter 6 points out that the visual cortex divides into two separate streams, called the dorsal (upper) and ventral (lower) stream. For our purposes, however, we can simply think of the visual brain as a stack of maps. This will become especially important when we consider the topic of attention, later (see Figures 8.11 and 8.31).

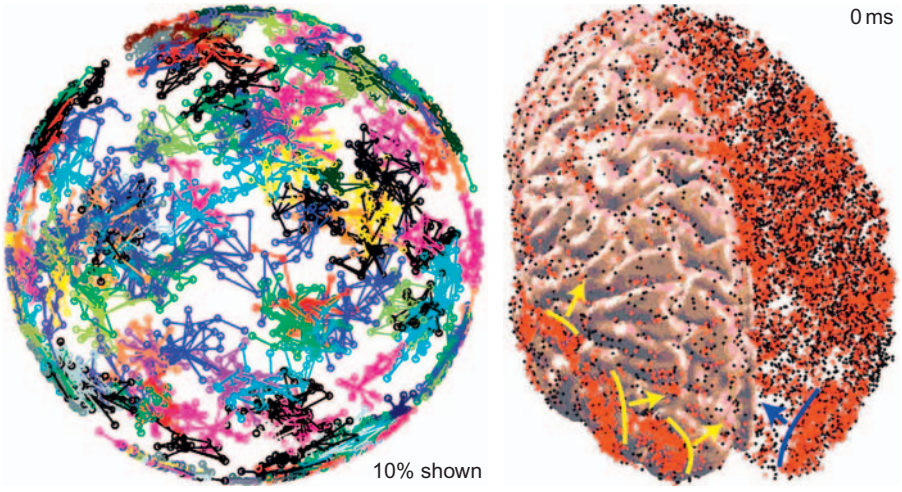

FIGURE 8.10C Spontaneous self-organization of cell assemblies in cortex. A large-scale active model of massive numbers of neurons and synapses in the cortex and thalamus. On the left, just 10% of the cell assemblies that emerged spontaneously in a large-scale model of 100 000 cortical neurons and 8.5 billion synaptic contacts. Eighty percent of synapses were excitatory, with 20% inhibitory links. Neuronal firing was simulated with millisecond precision. Neurons were connected 'reentrantly', with the two-way flow of activity that is typical of thalamocortical signaling. Axonal spikes take a brief time to propagate, depending on the length of the axon. This propagation delay was built into the model, and the Hebbian rule was applied that 'neurons that fire together, wire together' (Chapter 3). The modeled cell assemblies showed self-organization. Stable cell assemblies emerged spontaneously (marked with colors on the left side) along with regular cell population rhythms and time-locked activity. The model did not simulate external sensory input or motor output, but even purely internal signal traffic caused realistic brain-like patterns of activity to emerge spontaneously. *Source*: Izhikevich, Gally, and Edelman, 2004.

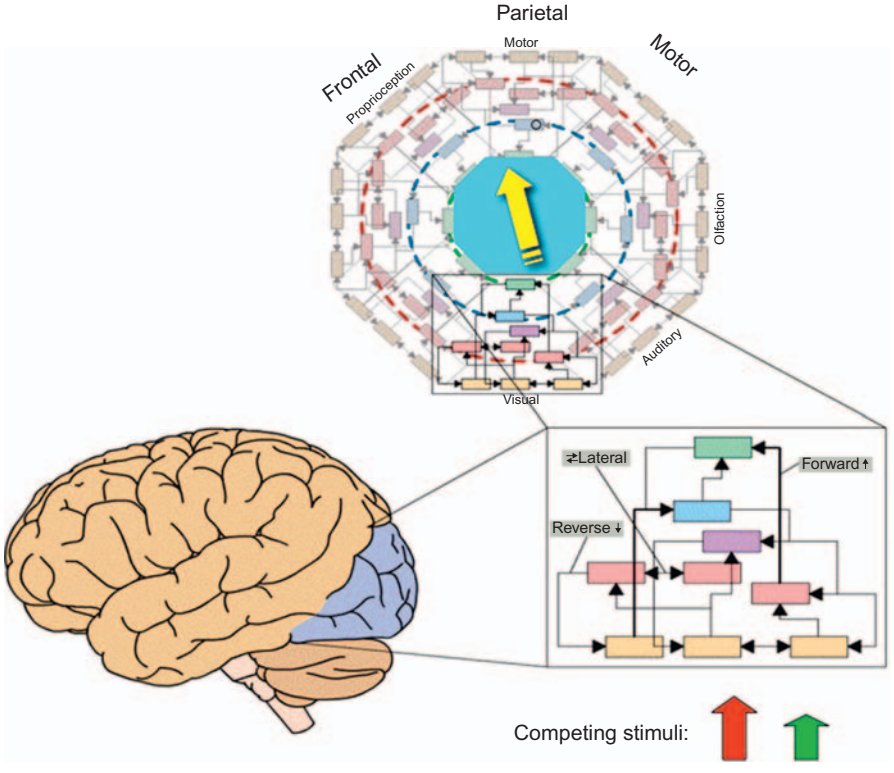

FIGURE 8.11 The cortex as a set of topographical maps. Cortical representations of vision, the body senses, motor output regions, and even hearing can be considered as hierarchies of maps (see Chapter 3). They are topographically related either to sensory surfaces like the retina, and/or to output arrays, like the motor homunculus of the cortex (see Chapter 5). Spatial mapping allows neurons representing different stimuli or output features at different levels of abstraction to ensure that they relate closely to each other if they refer to the same point in space or to the same part of the body. Such spatial mapping is complemented by temporal rhythms, which add the ability to coordinate corresponding regions of each map to a flow of events taking place over precisely specified moments in time. Together, topographical maps and oscillatory coding make possible many kinds of *spatiotemporal* codes in the brain. *Source*: Adapted from Friston, 2003.

1.7 Two-way connections

Most highways in the brain are two-directional. We tend to think of the visual system as a one-way flow of input, beginning at the retina, then flowing to the LGN, and then the primary visual cortex (V1) and so on. In fact, about 90% of the LGN-V1 fibers 'are running the wrong way'. Above the LGN everything is a two-way highway. This is a dominant feature of the brain, and it is a great challenge to understand how two-way connections work.

When the same topographical point is activated in two or more visuotopical maps, we are likely to get *reentrant signaling,* just as if many people with their own maps of a city were telephoning the same set of map coordinates to each other. Reentrant signaling sometimes is called 'resonant activity', and it is broadly consistent with the ubiquity of brain rhythms linking topographical maps. Regular rhythms and topographical mapping may be two sides of the same coin, a biological operating style that allows signals to be passed between similar points on many layers of maps. The body senses and motor output seem to work in much the same way, using topographical maps of the body and its surrounding space (see Chapter 5).

Reentrant loops between similar maps can strengthen or inhibit each other. If all the map readers in our metaphor agree on the coordinates of a location, your confidence in their reports will increase. Each confirmed message strengthens the combined signal and reduces errors and noise. But when map readers disagree on the coordinates, their information will tend to weaken each other. Active neuronal maps can engage in *inhibitory* interactions as well as excitatory ones. About 90% of the neurons in cortex are excitatory, but they could not function without numerous inhibitory neurons to regulate their activity levels, impose rhythmic pacing on excitatory activity, and sculpt inhibitory boundaries between excitatory islands of activity.

The theory of Neural Darwinism (ND) is consistent with this perspective, with the added point that in ND, topographical maps evolve over time toward a better and better fit of the sensory input or motor output (Edelman, 1989). In ND, neurons and synapses are strengthened if they make successful connections and weakened when they fail to do so. The same point applies to excitatory and inhibitory connections among competing populations of neurons. Like biological evolution, ND allows for 'fitter' maps to win out over 'less fit' ones.

As mentioned, brain maps *plus* rhythmic signaling constitute a *spatiotemporal* code. As we have seen, a television broadcast makes use of a spatiotemporal code. If you send a photo of yourself by cell phone, you are also using a spatiotemporal code. The brain must deal with the same engineering challenges that humans have learned to deal with using computers and telephones.

1.8 How neurons synchronize

Synchrony is a pervasive feature of the brain, apparently to coordinate patches of neurons at different locations. Indeed, synchrony appears even when neurons are cultured in a laboratory dish, or when a thin slice of the thalamocortical core is kept viable by growth factors. Synchronous activity appears to be a self-organizing feature of neurons in their natural environment. However, in the brain, synchrony has multiple signaling roles, and it appears to be under homeostatic control, like all other physiological parameters. The detailed workings of brain rhythms are still being studied.

When two brain regions fire in synchrony with a lag time, the term *phase locking* is more accurate than *synchrony*. Sound waves echoing in a canyon are phase locked but not synchronous, because they echo back and forth with a brief lag time. Because neurons also take time to send their axonal spikes, there is a lag time in echoing among related brain regions, leading to phase locking rather than synchrony. Both synchrony and phase locking are commonly observed in the brain.

Excitatory neurons can synchronize their firing when they are driven by a common inhibitory cell. Synchronized oscillations are believed to have many roles in the brain, in perception, attention, and memory (Figures 8.12 and 8.13). Synchronized groups of neurons firing at gamma rates tend to recruit additional neurons firing at the same rate (Llinas *et al.*, 2005)Faster rhythms are favored in this respect, because they allow for better temporal precision; beta and gamma provide neural 'clocks' that can detect small time differences compared to slower rhythms.

Synchronized group oscillations reflect the way individual neurons operate. Single neurons can accumulate inputs from other cells over about 10 milliseconds before they fire an action potential. If two neurons send their signals to a target neuron spaced more than 10 milliseconds apart, their effects simply fade before adding up to a new spike in the target neuron (see Chapter 3). This basic fact is believed to place an upper limit on the rate of neuron-to-neuron signaling. Relatively faster rhythms of the waking state, like theta, alpha, beta, and gamma, are in the right frequency range to recruit additional neurons.

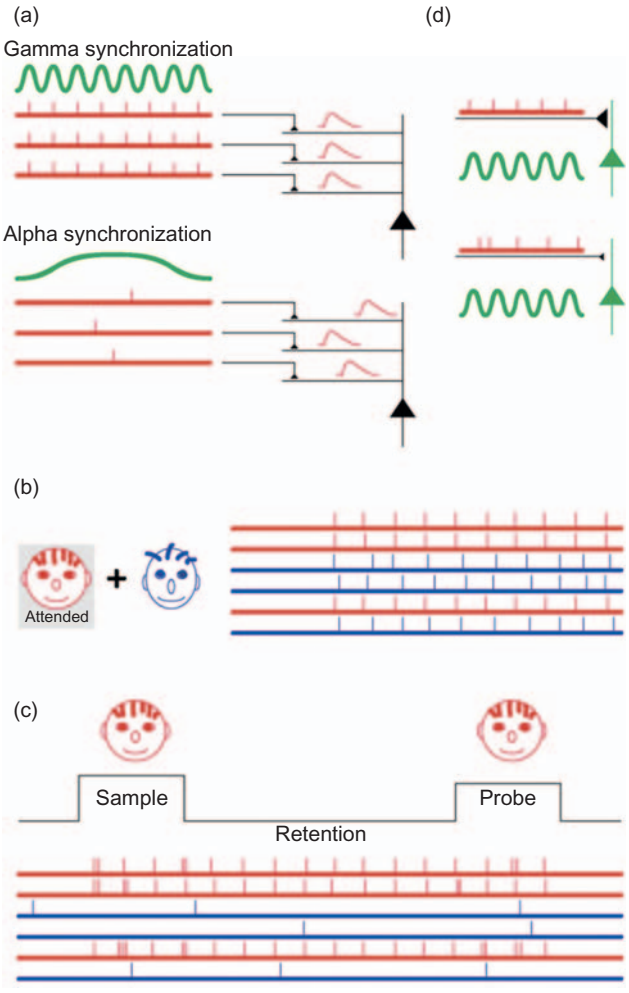

FIGURE 8.12 Synchrony in perception, attention, and memory. (a) Shows how several neurons firing at the same time can add up to a gamma wave in the electrical field potential. Gamma synchrony allows for finer temporal resolution than alpha. (b) Shows how attentional mechanisms might work by selectively enhancing populations of neurons that drive target neurons at gamma rates. If you are looking at the red face on a sheet of white paper, neurons that are sensitive to the difference between red and white, those that fire to high visual contrast, and those that pick up faces will tend to fire in synchrony to enable the brain to encode the red face. If you then decide to pay attention to the red face, your brain can add to the activity of those sensory populations by firing additional cells in synchrony with the red face–sensitive populations. The blue face will not receive these additional pulses of activity timed with its feature neurons and will therefore not be enhanced. (c) Shows how synchronized neurons may retain a dynamic memory of a visual stimulus for some time (seconds or minutes). The sample face triggers populations of feature-sensitive neurons that fire in synchrony with each other. When the sample face is removed, some of those feature neurons continue to fire for some seconds or minutes. When the recognition probe is presented, the relevant neurons are already primed to respond in synchrony to the recognized stimulus. There is direct brain evidence for such short-term memory mechanisms. *Source*: Jensen *et al.*, 2007.

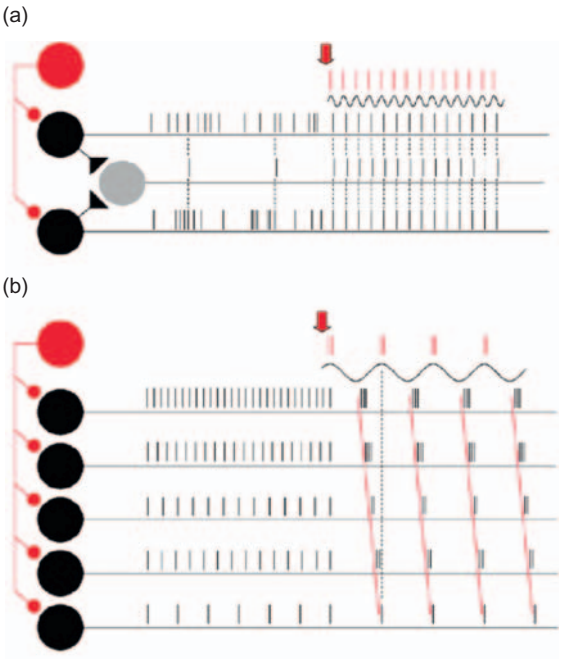

FIGURE 8.13 Inhibitory cells synchronize excitatory neurons. How inhibitory neurons drive synchrony in excitatory cells. (a) Coding by synchrony. If two excitatory cells (black) display random spike trains, they will rarely drive a common downstream cell above threshold (gray). By contrast, when synchronized by an inhibitory interneuron (red) these neurons, firing at the same overall rate, will now reliably activate the downstream neuron. (b) Phase coding. If five pyramidal neurons (black) are firing at different rates, the introduction of a rhythmic inhibitory cell will produce a rate-to-phase transform for the first spike in each cycle. The angled red line indicates the range of phase encoding made possible by this mechanism. *Source*: Mann and Paulson, 2007.

Regular population rhythms, like the ones we observe in the EEG, are believed to require both excitatory and inhibitory neurons. The pyramidal (excitatory) neurons of the cortex are surrounded by many inhibitory interneurons, which are needed to shape regular rhythmic waveforms. Figure 8.12a shows how neuronal firing adds up to gamma synchrony in the EEG or the local electrical field. Alpha synchrony is slower and therefore has less temporal precision.

In principle, attentional control regions in the brain can synchronize their output with target areas; for example, the attentional network discovered by Posner and coworkers may dance to the same beat as face-selective visual maps of the temporal lobe (Figure 8.31). Figure 8.12b shows that adding to the overall synchrony strengthens the red face signal and decreases the blue face activity by breaking up its synchronous input activity. Finally, in Figure 8.12c, a synchronous population

can respond to a stimulus and may keep running for some seconds or minutes after the stimulus has ended. Synchronous wave activity can therefore store a temporary memory, but it may fade fairly quickly and may also be vulnerable to interference from other stimuli.

These are only some of the coding possibilities of synchronous neurons and populations. Obviously, these are hypotheses that require supportive evidence, as we will see.

1.9 Synchrony for gain control

Gamma synchrony may amplify neuronal population amplitude because synchronized neurons can add to each other's activity. Synchrony tends to increase the size of the signal in much the way a microphone that picks up sounds from a loudspeaker will tend to amplify the signal over and over again. In biological systems, such self-amplifying feedback can never be allowed to run out of control for the same reason that sound systems can't allow infinite self-amplification. Audio systems have control circuits to prevent amplifier feedback from overloading the speakers, not to mention the ears of the listeners. Epileptic seizures may actually represent the wrong kind of self-amplification of slow rhythms, interfering with normal brain functions and even leading to a loss of consciousness.

We should not leave the impression that the waking state is *completely* synchronized at high frequencies. Rather, synchrony appears in local task-related patches of the brain, surrounded by nonsynchronized populations of neurons. If a task like vision needs to coordinate multiple visual maps, gamma synchrony may appear in multiple locations in the visual cortex (see Figure 8.23). Or as we will see later, if a conscious brain surgery patient has been asked to name a visual object, we may see transient gamma synchrony between areas for object recognition and speech production.

The raw EEG shows only the surface waves of a deep and turbulent ocean. Underneath the visible EEG there are multiple oscillatory streams interacting over a wide range of frequencies (0.01–1000 Hz have been observed). Some of these under-the-surface waves are locked in synchrony with each other, some of them are phase-locked, many are transiently coordinated, others show cross-frequency coupling. The metaphor of a turbulent ocean is a useful first approximation, but unlike the ocean in a biological brain, there are many *functional* activities going on all the time. Knowledge about the roles of brain rhythms is building at remarkable speed.

In Figure 8.14 the entire visual stimulus (a) can actually be seen as a candlestick or (b) as a single face looking toward us (c) or as two faces looking at each other. Thus, the identical physical input has three interpretations. Each perceived object involves a different figure-ground grouping. If object-sensitive neurons pick up the candlestick (Object 1), they can drive other neurons to synchronize with it and inhibit the other objects. The coalition of synchronized maps that fires the largest signal may either out-vote the nonselected objects,

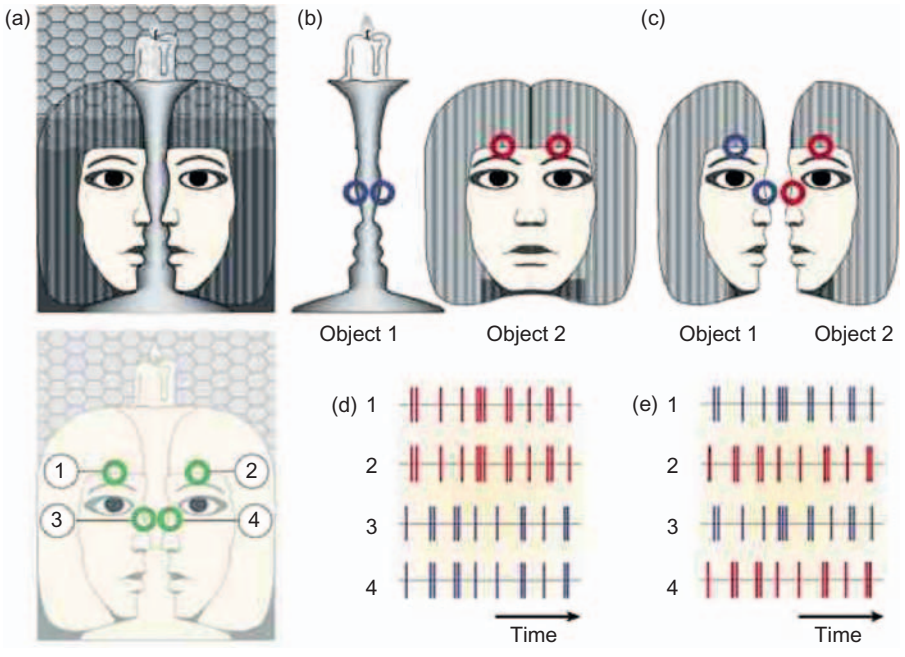

FIGURE 8.14 How synchronized neurons may bind sensory features. Brain rhythms may 'bind' (unify) multiple features of a visual stimulus into one coherent visual object. We know that the visual brain takes apart a physical stimulus into component features: location, color, pixel-level details, edge contrasts, and orientation, and ultimately, object identity (see Chapter 6). 'Object identity', like seeing a coffee cup as a whole, combines all those features into a single 'gestalt' entity. For that reason, object representation has been thought to 'bind' multiple visual features. This is sometimes called 'the binding problem'. It is associated with the question of visual consciousness, because we tend to be conscious of whole objects and events rather than isolated features floating in space. *Source*: Engel *et al.*, 2001.

or it may actively inhibit them (Engel *et al*., 2001). We will see direct brain recording evidence for synchronized firing of visual feature sensitive neurons below (see Figures 8.15 and 8.16).

Some authors suggest that all brain oscillations – waking, dreaming, and sleeping – are carried or multiplexed by very slow oscillations, cycling at less than 0.5 Hz (Steriade, 2000). As we will see, there is direct evidence for multiplexing of gamma waves on theta and perhaps gamma on alpha as well. Since the gamma range is expanding to 120 Hz, 200 Hz, or even 1 000 Hz, it seems likely that we will see many more kinds of multiplexing in the brain as recording techniques improve.

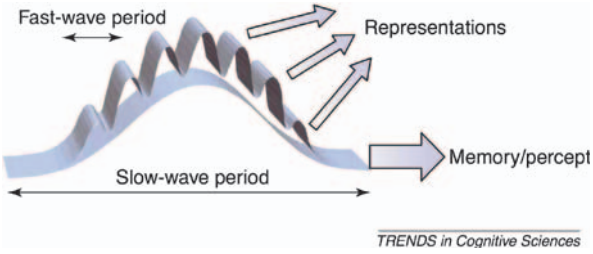

FIGURE 8.15 Multiplexing faster waves on slower ones. Fast waves may 'multiplex' on top of slower waves, like the amplitude modulation of radio signals. This is known by several other names. It appears to be a common coding strategy in the brain. *Source*: VanRullen and Koch, 2003.

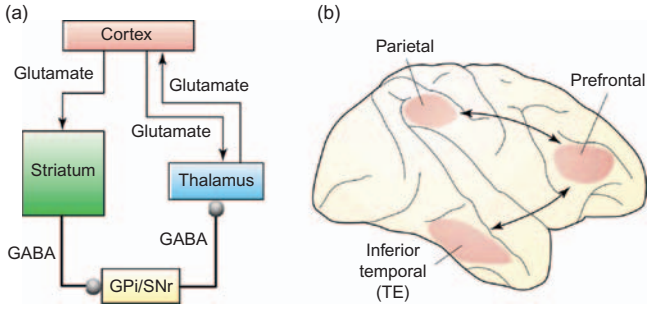

FIGURE 8.16 Waking: Stimulus-specific reverberation during early learning. A dynamic neural circuit for the first phase of learning. During the waking state, working memory is believed to be sustained by a recurrent circuit, including cortex, thalamus, and basal ganglia (striatum), enhanced by neuromodulation originating in the substantia nigra (SNr) and globus pallidus (GPi). While visual input enters the cortex in the occipital lobe, integration of visual objects is believed to occur in the inferior temporal lobe (called area TE in the macaque brain, shown here). Parietal involvement is required for spatial localization of visual events in body space and for manual reaching and manipulation. Prefrontal involvement is required for overall integration, voluntary attention, and motor control (executive functions). Notice that glutamate and GABA are the two major neurotransmitters shown. Stabilization of this circuit may require NMDA receptors for increasing the efficiency of active synapses. The hippocampal complex (not shown) is required for episodic learning and, over time, for semantic memory. Memory consolidation during SWS is needed to make enduring memories by protein synthesis which makes new synapses and other cellular structures needed to sustain long-term memory. *Source*: Wang, 2001.

The basic advantage of multiplexing is to lower the firing threshold of downstream neurons by reducing their membrane polarity (see Chapter 3). Thus, theta waves may spread to some target population and make them slightly more sensitive, after which added gamma waves may push them over the firing threshold. If the target neurons are able to follow the input at gamma rates, they may then produce their own synchronized gamma burst, which may in turn 'ignite' a larger population of neurons. For example, VanRullen and Koch (2003) have shown that visual signals can be detected better if they occur at the peak of the endogenous alpha wave. One plausible explanation is that many regions of the visual brain oscillate at alpha rates during resting states, and that the baseline voltages of large numbers of neurons are gently being raised and lowered at 12 to 14 Hz. Certainly that is the view of slow oscillations propounded by Steriade (2000) and others.

The cortex appears to have a number of microcircuits that can perform more complex computations like coincidence detection and even elementary logic and arithmetic operations like the ones that are built into basic computer chips (Gabbiani *et al*., 2002). The present discussion is focused on only basic oscillatory aspects of neural computation.

We will now look at some details of how the thalamocortical core of the brain works in the three major states.

2.0 WAKING

The contents of our waking consciousness include the immediate perceptual world; inner speech and visual imagery; the fleeting present and its fading traces in immediate memory; bodily feelings like pleasure, pain, and excitement; autobiographical memories when they are remembered; clear and immediate intentions, expectations, and actions; explicit beliefs about oneself and the world; and concepts that are abstract but focal. Obviously, we are conscious of much more than we report at any given time, but humans can answer questions about a remarkable range of conscious events – the sight of a single star on a dark night, the difference between the sounds 'ba' and 'pa', and the goal of studying for an exam. All sensory systems do a great deal of unconscious processing, leading to conscious, reportable sights, sounds, and feelings.

Recalling an autobiographical memory also results in conscious experiences, like your memory of seeing this book for the first time. Inner speech and imagery have conscious aspects. Asking someone to rehearse a list of words usually results in conscious inner speech. People vary in the vividness of their visual images, but dreams, for example, are classically reported to have vivid imagery (Stickgold *et al*., 2001). Finally, action planning can have conscious components, especially when we have to make choices about our actions (Lau *et al*., 2004a, 2004b). Normally, we may not have to think much about the action of walking, but if we break a leg, even standing up and walking can become a consciously planned process (Sacks, 1984).

There is good evidence that we have a spontaneous inner flow of conscious contents that constantly compete against the perceptual world (Singer, 1994; Mazoyer *et al*., 2001; Fox *et al*., 2005). In sum, in everyday life, there is ongoing competition between inner and outer events, between perceiving and responding, and between simultaneous input streams. Attentional selection seems to operate every moment of the waking day.

2.1 Realistic thinking

While dreams are notoriously unrealistic, waking consciousness has long been considered to be the realm of logical, mature, reality-oriented thought. There is considerable truth to that, even though we also commonly engage in waking fantasies, daydreaming, emotionally driven thinking, and mind-wandering. It is notoriously difficult to focus on just one task with full concentration, and there may be good biological reasons for that. Humans did not evolve in a world of classrooms and book learning. Paleolithic hunter-gatherers had to be constantly alert for unexpected dangers and opportunities; focusing completely on one thing to the exclusion of all others would have been dangerous. Humans have a tendency to lightly scan the sensory world, rather than doggedly following a single goal or a single train of thought. At the same time, our large brains give us enormous adaptability. We can learn to control our attention, at least for some period of time, and traditional cultures train children in cognitively demanding tasks like hunting, path-finding, identifying hundreds of plants, traveling long distances, making tools, preparing food, and adhering to numerous social customs. Those habits require learning and executive attention. They also place a premium on understanding the world realistically. However, the brain basis of 'realism' has not been studied sufficiently so far. As a result we do not understand how we can watch a horror movie without being frightened (because we know it is an illusion) and compare that to realistic experiences. Given the tools we have today, that question can be addressed empirically.

In a precarious world it requires self-control not to allow feelings like fear, hunger, loneliness, or anger to take over. Children in hunter-gatherer cultures often are trained to endure privation and emotional stress. Our brains evolved to cope with such conditions. It is only very recently that human beings have lived more secure lives, with reliable sources of food, social support, and protection from danger and discomfort.

The waking brain has been described as being 'poised on the cusp of a transition between ordered and random behavior' (Table 8.1). This delicate state 'optimizes information transfer and storage … (including) both prolonged periods of phase-locking and occurrence of large rapid changes in the state of global synchronization…'. (Kitzbichler *et al*., 2009). The waking thalamocortical state is optimized to combine such capacities. Rhythmic synchrony and phase-locking allow the brain to relate different time scales to each other. Thus, the piccolo of the brain orchestra can play in rhythm with the bass drum.

The last decade has seen an avalanche of findings on brain rhythms in the sensory and motor systems in the hippocampal memory system, selective attention, and executive control. These findings come from direct brain recordings in animals and humans, from EEG and MEG, and from combining these electromagnetic

TABLE 8.1 Major features of the conscious waking state

1	Very wide range of conscious contents
2	Widespread brain effects *beyond* the specific contents of consciousness
3	Informative conscious contents
4	Rapid adaptivity and fleetingness
5	Internal consistency
6	Limited capacity and seriality
7	Sensory binding
8	Self-attribution
9	Accurate reportability
10	Subjectivity
11	Focus-fringe structure
12	Consciousness facilitates learning
13	Stability of conscious contents
14	Object and event-centered
15	Consciousness is useful for voluntary decision making
16	Involvement of the thalamocortical core

Source: Seth and Baars, 2005.

recording methods with the spatial advantages of fMRI. Interlocking rhythms have been observed in single neurons, in neuronal circuits and arrays, and even in entire brain lobes. Rhythmic activities in the core brain are the most obvious markers of different states of consciousness, and recent evidence suggests that attentional selection operates by way of synchronized brain rhythms as well. The slow oscillatory state of deep sleep seems dedicated to consolidating memories of the conscious experiences of the preceding day. As we will see, even sleep seems to utilize fast rhythms during the peak of slow delta wave to consolidate the conscious experiences of the preceding day.

Table 8.2 lays out various kinds of consciously mediated cognition – pretty much all processes we study. Notice the unconscious aspects of these partly conscious tasks. Both conscious and unconscious components are likely to be crucial for normal, flexible, adaptable cognition. However, subliminal perception and learning, for example, may take place for highly significant and stereotyped stimuli.

2.2 Orientation to place, time, and persons

Our basic knowledge about conscious experiences comes from what people can tell us (see Chapter 2). When a patient with possible brain damage is clinically examined, a neuropsychologist will begin by administering a 'mini-mental status exam'. It spells out what we expect from a conscious person with a healthy brain (McDougall, 1990):

1. Orientation to time, place, and person: 'What day of the week, date, and season is it'? 'Where are you now'? 'Who are you'? 'Who am I'? [the examiner].
2. Simple working memory: 'Remember these three objects …'.
3. Attention and calculation: 'Count down by sevens starting from 100' (100, 93, 86, 79, 72 …).
4. Intermediate recall: 'What were the three objects I mentioned before'?
5. Language: Ask the patient to name a wristwatch and a pencil, to repeat a sentence, to follow three simple commands, to read and understand a simple sentence, and to write their own sentence.
6. A basic visuomotor skill: Copying a drawing of a line pentagon.

Notice that normal voluntary control is implied by all of these tasks. People with frontal lobe deficits may have difficulty doing them because of impaired executive functions. As basic as the questions may seem, they cover sensory perception, voluntary control, working memory, immediate and intermediate memory, long-term retrieval, mental effort, language, attention to daily events, regular updating of memory as time goes on, mental imagery, spatial skills, and more. All these tasks require both the waking state (alertness) and consciously mediated cognition. They are impaired by drowsiness, attentional lapses, SWS and REM dreaming, as well as by drugs and brain disorders that impair consciousness.

Normal waking is the necessary condition for all the cognitive processes we discuss in this book.

TABLE 8.2 Consciously mediated cognition

Task	Conscious aspects	Unconscious aspects
Working memory	Sensory input, response planning and output, momentarily mentally rehearsed item	Preperceptual, unrehearsed, basal ganglia
Spontaneous problem-solving	Problem definition, realizing the solution (the'Aha'! experience)	Problem incubation
Sensory feature binding, posterior cortex	Results of binding	Detailed process of integration
Sensory-spatial integration, parietal lobe	Same	Same
Sensorimotor skills (e.g. speaking)	Acquisition phase and making changes in routine tasks	Predictable components after extensive practice
Comparing conscious experiences that occur at different times	Novel memories, and novel relationships	Well-established memories and procedures
Voluntary attention	Effortful control of attention, or maintaining attention against contrary tendencies, such as fatigue, drowsiness, or more attractive topics of attention	Routine, automatic, noncompeting, and highly predictable control of attention
Automatic attention	The results of attention are commonly conscious (but not always)	Detailed control of automatic attention
Implicit learning	Conscious cues to the implicit regularities or inferences	Automatic or implicit information to be learned

2.3 Waking is for learning; sleep enables memory consolidation

Although waking is by far the best time for learning, sleep and REM dreams enhance memory consolidation. Memories are believed to be unstable and vulnerable to interference in the early hours after learning. Early memory is thought to depend upon active, resonating neural circuits (Figure 8.16). However, some researchers believe that waking may also allow some memory consolidation. After about a day, learned material appears to be 'consolidated' – made more enduring – a process that is thought to require protein synthesis. Lasting memories involve structural changes to synapses and cells and sometimes to entire brain networks. Sleep appears to enhance memory consolidation by protein synthesis, which requires gene expression in numerous brain cells.

Although all states of consciousness have multiple functions, the conscious waking state is by far the most adaptable one. As we will see in Chapter 9, every region of the brain has its own ability to adapt and learn. Therefore, there are many kinds of learning. But to explore new kinds of information and commit them to memory, we are constantly making things conscious. In everyday life, that's what we mean by 'paying attention'. Memory researchers point out that most of our learning is 'incidental'; that is, it occurs as a benefit of paying attention (Kristjánsson, 2006). We are learning during most of our waking moments, as we can show by using sensitive measures of episodic (experiential) memory. But we are certainly not deliberately memorizing things in every waking moment. *Memorizing* is only one way to make learning happen. Most of the time it seems that we learn things just by paying attention to them – which means becoming conscious of them. Memory researchers since Hermann Ebbinghaus have pointed to the central role that conscious attention plays in normal learning. Although there is some evidence for unconscious acquisition of information, we will focus on the powerful role of conscious attention in mobilizing hippocampal and cortical mechanisms of learning (see Chapter 9).

2.4 Attention and consciousness commonly enable learning

How is it that you can learn the material in this book? Human beings really do not know. What we do in daily life is simply *pay attention* to new and interesting things – exploring them with our senses, rehearsing them mentally, and repeatedly directing our attention to them – and magically, learning seems to occur. The next day, we suddenly realize that yesterday's new information seems more familiar. We must have learned it. Orienting tasks are important to enable learning. 'Mere exposure' to information is often enough to enable recognition memory. In cognitive science jargon, most of our everyday learning is *incidental*.

What we generally do is just pay attention to new material, even if it seems hard to understand. The biggest challenge is to pay attention to new and difficult information and to be patient enough to allow our brains to wonder, ask questions, and, ultimately, comprehend any new material. Once we perceive and comprehend something new, learning seems to occur. Brain evidence indicates that spontaneously paying attention to some sensory content also activates the hippocampal complex (Stark and Okado, 2003).

We *can* direct our attention voluntarily, although it sometimes takes a noticeable effort to do so (see Chapter 12). Selective attention generally leads to conscious experiences (earlier), and it seems to be the act of making things *conscious* that enables learning. Indeed, 'episodic and declarative learning' are defined as 'learning of conscious events', and we know that the hippocampus seems especially adapted for that (Squire *et al.*, 2008; see Chapter 9). Though there is reliable evidence for subliminal perception and learning, we will limit this discussion to episodic and declarative memory of conscious events.

Cognitive neuroscientists believe that declarative and episodic learning generally occurs something like this (Seitz and Watanabe, 2005): We pay attention to new information so that it tends to become conscious. As soon as we experience the new information with enough clarity, our brains are able to store it. Repeated attention to new or difficult material often is needed before we get a sense of clarity. By using sensitive measures of episodic and declarative (conscious) memory, like recognition measures, we can show that humans learn very quickly after clear conscious experiences of new information. There is reliable evidence for subliminal learning, but here we will focus on learning of conscious events, or of material that is cued by conscious events.

That does *not* mean we can *recall* all memories on cue. It does mean that we can *recognize* consciously experienced events far above chance. Recognition tests are easy because they simply reinstate the same experience we had before. We don't have to voluntarily search our memories at all. All we have to do is say,

'Yes, I've seen it before', or 'No, I haven't'. Simple conscious experience of the material to be recognized will trigger automatic memory search. The yes/no decision is made by means of familiarity.

For example, you may be surprised to recognize a scene in a movie you may have seen 10 years ago. It wasn't necessary for you to memorize the movie scene. All you had to do was to watch it once – consciously – and then see it again 10 years later. Consciousness of an event seems to be enough to establish it in memory. Much the same is true of recognizing yearbook photos of high school classmates, news photos, headlines from years ago, and the like.

Unfortunately for students, academic exams rarely use recognition tests. Rather, exams test *associative recall* by asking questions like, 'What is the capital of France'? College exams would be a lot easier if they gave us a part of the answer, like the partial recognition item: 'Par… is the capital of France'.

Associative recall tests give much lower estimates for accurate memories than recognition tests. That is why academic exams are difficult: It is therefore not our stored memories that are at fault but our ability to retrieve them on demand. By analogy, you can file a book randomly in a giant library. The book (the memory) is somewhere in there, but you cannot retrieve it on demand unless you have a very good retrieval system, like a search engine or a card catalog. Otherwise, the book might as well be lost forever.

Notice that simply paying attention does not always make things conscious. For example, we can pay attention to an ambiguous figure without seeing one of its interpretations (see Chapter 1). As a result, we may never learn the nonconscious interpretation of the figure as a conscious, episodic memory. Learning a complicated subject like brain science is often like learning an ambiguous stimulus and never quite seeing the unaccessed interpretation. At first, new material may seem vague, hard to understand, or confusing. Then we may spend some time thinking about it, paying attention to it, trying to draw it by hand, or answering questions about it. Over time, a clearer sense of meaning tends to come. At the point when we become clearly conscious of the desired information, learning tends to follow quickly. Most of our effort in studying new material is therefore devoted to the task of comprehension. Once we understand things clearly, memory tends to come along.

In sum, paying attention may be a means toward conscious clarity, which in turn enables episodic and declarative learning. The hippocampal complex is believed to turn conscious experiences into memories. At first, hippocampal memory is believed to be unstable, or *labile*. Consolidation serves to make long-lasting changes in the hippocampus and to transfer learning to the neocortex. Theta oscillations are believed to play a major role in both local hippocampal functions and in long-range coordination between the hippocampus and neocortex.

2.5 Losing consciousness of predictable routines

Although paying attention to a stimulus often leads to different ways of experiencing it, there is a fundamental case where the opposite happens: The case of practiced habits. As a rule, the more predictable a sensorimotor skill becomes, the less of it will be conscious. That is a common-sense observation about learning to ride a bicycle and even learning to speak a new language. The fading of conscious access to habitual skills is commonly called 'automaticity' and it goes along with a loss of precise voluntary control over habitual details (see Chapter 2, Section 5.1).

The world around us becomes more predictable as we grow up and learn to understand it. If everything were completely known and predictable we might not have to pay attention at all. Our brains could just go on automatic. Fortunately the real world is full of changes and challenges, and we find ourselves constantly choosing the most important and novel events to pay attention to. The stream of consciousness is all about our personal news headlines. We tend to dwell on whatever is novel or significant to us.

Repetitive events tend to fade from consciousness unless they have special significance. The itch of a mosquito bite may not fade quickly, because the saliva of the female mosquito triggers the pain system. Pain is inherently significant, like hunger or the taste of chocolate. We do not habituate rapidly to biologically significant events, but neutral ones can fade quite rapidly, sometimes in seconds. Even though gravity constantly triggers our vestibular (balance) sense, we rarely pay attention to it because it has become predictable. The body in relation to gravity becomes a focus of attention again for astronauts, parachute jumpers, and children riding a Ferris wheel.

Schneider (2009) writes that

> The concepts of automaticity, controlled processing and consciousness are tightly coupled … . Automatic processing … supports parallel, low effort processing that is difficult to control. Controlled processing

operates from a set of 'domain general' areas that exhibit serial effortful processing in novel or changing situations.

(However), automatic processes in the form of automatic *attention* can activate conscious awareness to stimuli that have been unattended.

The last point is very important. We lose conscious access to automatic routines, but some of them are attentional routines – that is, they function to bring things to consciousness. Automatic eye movements are a good example. Many eye movements are automatic, and as they bring a moving truck into our field of vision, the sight of the truck becomes conscious.

In those cases, of course, automaticity actually enables important information to become conscious. But more generally, practice leads to automaticity and a drop in conscious access to the highly practiced skill. Much of our ordinary mental life recruits automatic routines that are invisible to us, but which enable all of our daily activities.

Brain studies of practiced skills show that cortical fMRI declines drastically when the skill fades from consciousness. Figure 8.17 shows a single subject's brain scan before and after learning a predictable auditory search task to the point of automaticity. As a result of practice and learning, the fMRI (BOLD) signal of an entire network of cortical regions is observed to drop below detection threshold. Such marked drops in cortical activity commonly are found in highly practiced, predictable tasks.

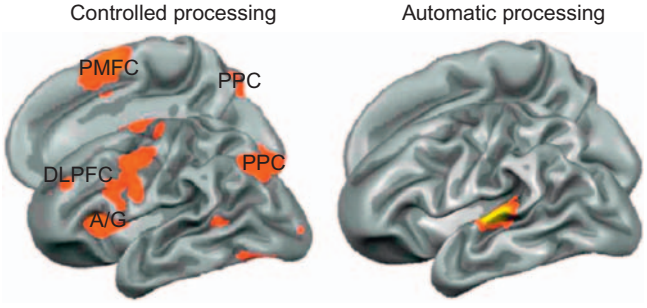

FIGURE 8.17 fMRI activation before and after practice. Controlled and automatic versions of the identical task can be compared in the same subject. When the auditory search task is novel it allows more detailed voluntary control, more conscious access, and more widespread cortical activation. Cole & Schneider (2008) have shown that voluntary control processing involves a network of domain-general areas of cortex, shown above. They naturally divide into frontal lobe activations (in front of the central sulcus) and BOLD activity in the posterior part of the parietal lobe. The same frontal and parietal regions are active in conscious, compared to unconscious, stimulus processing. These areas are called 'domain general' because they function in different tasks, using visual or auditory stimuli, with either simple or complex stimuli and tasks. *Source*: Schneider, 2009.

Notice, however, that a part of the auditory cortex remains active even after the scanning task becomes automatic, namely the upper rear ridge of the posterior temporal lobe. The reason is that the auditory input continues to be analyzed. However, the local cortical activation does not seem to spread widely, as fully conscious events seem to do (see Figure 8.17).

Figure 8.17 raises some important questions. One is about the voluntary control network, which we discuss in more detail in Chapters 11 and 12. As you might expect, a number of control-related regions of cortex cluster around the motor strip, just in front of the central sulcus. They include the dorsolateral prefrontal region (dl-PfC), a part of the insula (anterior insula), pre-supplementary motor cortex (PMC), dPMC (dorsal premotor cortex), and the inferior frontal junction (IFJ). Just over the top of the hill of the hemisphere, we see activity in premotor cortex (dorsal part) and in anterior cingulate (AIC). It is easiest to think of all these regions as different levels of motor maps, some very specific to the muscles, and other at higher levels, including simply the 'urge to move'. DL-PFC is involved in all effortful voluntary tasks. Notice also that in the speaking hemisphere these regions border on Broca's area, the speech production region of cortex, which is positioned close to the motor cortex for the mouth and tongue. These frontal regions have complicated names, but they follow a simple rule because they are all frontal, and intimately involved with action control.

Notice that these frontal areas use both faces of each hemisphere, the lateral (outside) and medial (inside) surfaces. Essentially they cover both hillsides of the same hill. Because the cortex is basically one large surface, its hills and valleys are not as important as the continuous surface itself.

Finally, we see BOLD activity to the rear of these frontal areas, in PPC, the posterior parietal cortex. You can think of this region as the action planning center before the human frontal lobe bulged out as far as it has, since earlier primates. Since the brain contains its own history, we can think of the human brain as having two action control centers, both of them feeding into the motor strip, which has the most direction connections to motor nerves traveling down the spinal cord and the cranial motor pathways to control the face, head, and neck. Because the vast forward expansion of the frontal lobes is quite recent (on an evolutionary time scale) we use both posterior parietal

and prefrontal control centers. The posterior parietal cortex is involved in planning, mental imagery, and sensorimotor integration. All those functions participate in controlled (voluntary) processes, and become less prominent when a practiced, predictable task becomes less conscious (Coulthard *et al*., 2008).

In the automatic task on the right side of Figure 8.17, has the brain stopped processing the auditory search task at all? Clearly not. While cortex is much less active, automatic routines are controlled by the basal ganglia, cerebellum, and spinal circuits. They may still use sensory input, as indicated by the active auditory cortex. But such highly practiced loops can apparently become almost entirely subcortical. It is just unconscious or much less conscious, with less detailed voluntary control and less cortical activity.

2.6 Implicit learning requires consciousness, too

The term *implicit learning* can be misleading. It does not mean learning without consciousness. Rather, implicit learning involves conscious input, leading to implicit (unconscious) inferences that are learned, along with the conscious aspects of the task.

When we practice a complex sensorimotor skill, as in sports, dancing, typing, reading, or musical performance, we do not become conscious of all the details of the task. Rather, we make only a part of the task conscious and allow automatic aspects to be recruited unconsciously. What scientists call 'explicit', 'episodic', or 'declarative' learning involves conscious learning – but there is no *exclusively* conscious learning. Conscious and unconscious processes always go together. What is technically called 'implicit (unconscious) learning' often comes as a side effect of conscious input. Conscious events may generally guide the learning process, even for implicit learning.

For example, the grammar of our first language is learned implicitly (unconsciously). Young children acquire language with remarkable speed but without having to know explicitly which words are nouns, verbs, or adverbs. Children do pay attention to new words and sentences and certainly become conscious of them when they speak and listen. Good caregivers constantly call kids' attention to new words and new experiences. Thus, consciousness is constantly involved in language learning, but the regularities of grammar seem to be learned *implicitly,* as a side-benefit of paying attention and making things conscious.

2.7 Fast rhythms coordinate waking tasks

The raw EEG of waking often is called 'beta' or 'gamma' activity, but it is in fact a complex and variable mix of many periodic and nonperiodic signals. We can think of the raw EEG as a choppy sea. In science, the ability to analyze complex waveforms at high speed is a recent development, dependent on powerful computers using Fourier analysis and similar techniques. As a result, current scientific articles rarely refer to the raw (unanalyzed) EEG any more. That can lead to real confusion, because we still tend to think of EEG in terms of pure waveforms. To follow the most recent practices, when we refer to 'beta' or 'gamma', we really are talking about a *band* of frequencies, beta being about 13 to 25 and gamma, 26 to 120 or so. There is no perfect agreement on the boundaries between standard frequency bands, and there probably should be no rigid numbers until we have a better understanding. New studies keep expanding to new wave bands that play important roles in the brain. For example, recent work shows that very–high frequency bursts are important (up to 1000 Hz) and that very–low frequency waves, down to .01 Hz, are also present in both waking and sleep. Keep in mind that brain rhythms are a moving target, as new evidence appears with remarkable rapidity.

Evolution constantly reutilizes biological mechanisms for new functions. Ancient parts of the brain, like the hippocampus – part of the reptilian small brain – already show both gamma and theta waves (4–7 Hz). It is likely that the neocortex, the vastly expanded 'new cortex' of mammals, borrowed and made novel use of those ancient rhythms. The major brain rhythms are found very widely in the animal kingdom. They are highly conserved among species and therefore likely to be important.

High levels of gamma oscillations have now been observed for sensory processing, attentional enhancement of sensory input, and both working and long-term memory. More recent work shows both high intensity of gamma activity and gamma *synchrony*, the simultaneous up-and-down rhythm of two different brain regions at frequency rates above 20 to 30 Hz. Synchrony is both natural and useful for signaling purposes in an oscillatory system like the brain. Sometimes perfect synchrony is not attainable, so that there is a brief time lag between the peak of the wave in one place (like the hippocampus) and another place (like the frontal lobe). In those cases, the better term is *phase locking* or *phase coherence*, a little bit like a syncopated 'off-beat' rhythm in music. It is synchrony with a time lag.

Individual neurons have a temporal integration time of about 10 ms, the period when dendritic inputs can add up to increase the probability of a single axonal output spike (see Chapter 3). A group of interconnected neurons can strengthen each other's firing rates between 30 and 100 Hz by supplying synaptic inputs within the 10-ms window. If two excitatory neurons are signaling each other at a rate of 50 Hz, for example, it is possible to sustain an excitatory feedback loop, because converging signals can arrive within the critical 10-ms period. However, neuronal firing rates below 30 Hz may not be integrated by target neurons, because different spikes may arrive too late to have additive effects. It is therefore believed that a group of neurons firing in the beta-gamma range will exert a stronger drive to downstream neurons than lower frequencies. Obviously, real brain networks are more complex and have inhibitory as well as excitatory elements. Nevertheless these basic points apply to neurons in general and have gained a good deal of direct empirical support.

Radio transmission has some similarities to oscillatory synchrony in the brain. Traditionally, the powerful electromagnetic waves used to broadcast radio use either frequency modulation (FM) or amplitude modulation (AM). In both cases, a fundamental frequency (the number on your radio dial) acts as a carrier wave for faster changes in frequency or amplitude, which reflect the voice or music signal. In your radio receiver, an electronic circuit is tuned to the frequency of the broadcasting station, and it is able to filter out the added, modulating signal that rides on the carrier wave. You end up listening to the songs and never hear the carrier frequency.

These similarities are not accidental. They reflect the basic physics of waves, which apply to brain rhythms as well as electromagnetic radiation. The existence of AM and FM radio suggests at least two ways in which brain rhythms may process information in the brain. But there are many more coding schemes. Brain rhythms could serve as clocks, and they can use single pulses or a series of pulses like Morse code. Different neurons may use signals in different ways, perhaps in combination with different molecules and synapses.

Television is an example of a *spatiotemporal* code, in which the broadcast signal scans across every line of the screen from top to bottom. Computer screens use similar spatiotemporal coding. Brain rhythms are also likely to coordinate visuotopic maps, somatotopical maps, and motor maps. As we have mentioned, the brain is rich in topographical maps, which represent sensory input arrays or neuromuscular maps at various levels of abstraction (see Chapter 5).

Evolution has exploited the rhythmic properties of neurons over hundreds of millions of years. For that reason, we should not expect to find only a single neural code. What we do know currently is that brain rhythms are very widespread and that they are associated with known functions.

Finally, waves can also interfere with each other. When you place a radio receiver next to a computer, you will hear a burst of noise whenever you press the keyboard. That is because each key press triggers an electromagnetic signal that radiates into the surrounding space. Wave interference is a fundamental phenomenon in the physics of radiation. Interference may have important uses in the brain, but it might also degrade neural information processing. We are only beginning to understand the role of brain rhythms, but it is likely that wave interference will turn out to have observable effects as well.

2.8 Gamma activity has multiple roles

Figure 8.18 shows a classic study of gamma activity in visual perception, using direct brain recording of electrical activity on the cortex. Intracranial EEG (iEEG) has a far better signal-to-noise ratio than scalp EEG, since it is recorded from the brain itself. iEEG voltages typically are measured in millivolts; scalp EEG is measured in microvolts. For that reason iEEG has major advantages. The great drawback is that it requires invasive surgery. Animal studies often use intracranial electrodes, but human iEEG is limited to patients with a compelling medical need. Epilepsy surgeons use iEEG to localize seizure-triggering brain regions and for locating areas of the cortex that must be protected to avoid harming essential functions, like language and vision. Patients are conscious during this kind of brain surgery so that they can answer questions and report their experiences. The cortex itself does not have pain receptors, and local anesthetic at the site of the incision may be enough to minimize discomfort. Thus, the patient is normally conscious, even though his or her brain activity is constantly recorded and stimulated directly at the cortex (Crone, 2006; Canolty, 2006).

Tallon-Baudry and Bertrand (1999) asked conscious patients with iEEG brain implants to report the presence of a visual triangle. Initially only real triangles were presented, evoking the two major gamma-range bursts of activity marked with the yellow color in Figure 8.18. On the upper graph in column B, notice that two (yellow) gamma bursts appear immediately after stimulus presentation (time = 0). The first gamma

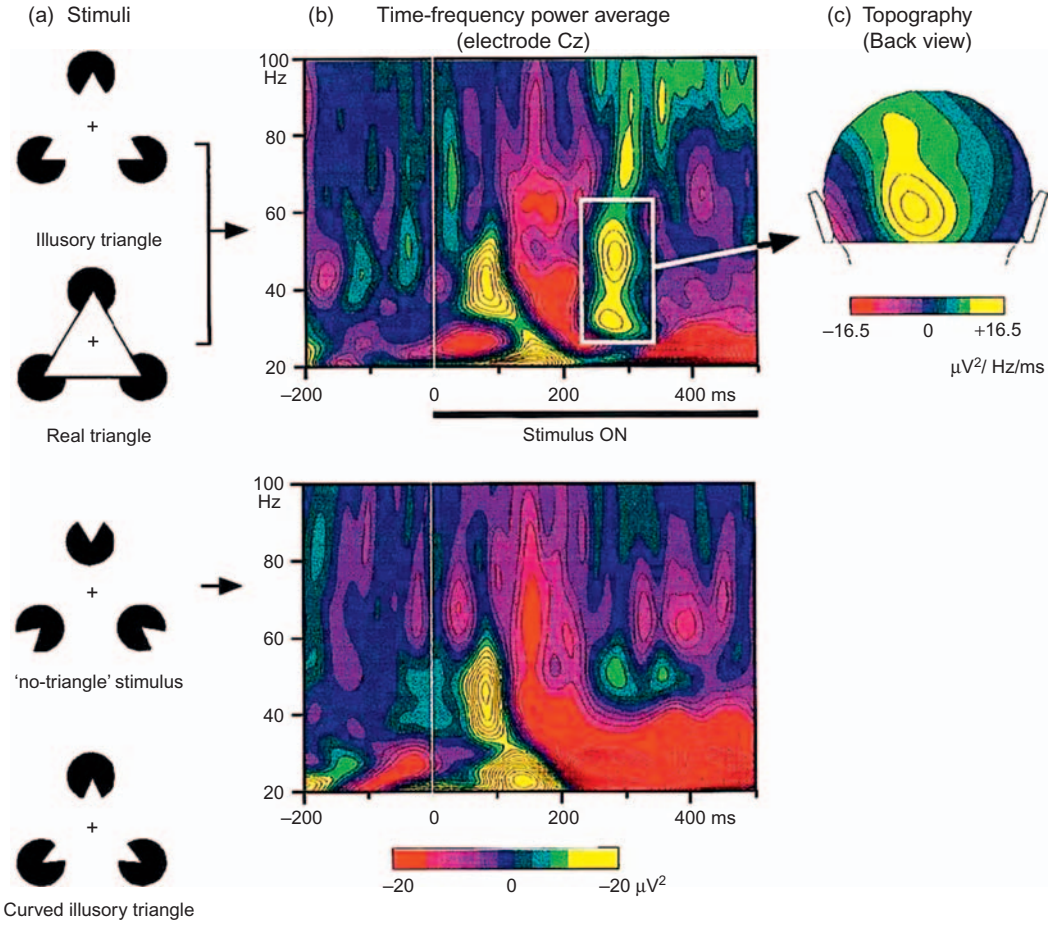

FIGURE 8.18 Evoked gamma bursts reflect visual feature binding. In a breakthrough experiment, Tallon-Baudry and Bertrand (1999) showed high gamma activity (yellow bursts) in the iEEG (direct brain recordings) of epileptic patients asked to report the appearance of a visual triangle. Two bursts were observed, one that occurred at stimulus presentation and a second that discriminated between triangle recognition and nonrecognition. Triangle recognition occurred with both the real triangle and the illusory triangle but not the 'no-triangle' stimulus. Both gamma bursts plausibly involve conscious and unconscious aspects of vision. The silhouette of the head (c) shows the distribution of the second gamma burst over the occipital and some parietal cortex. *Source*: Tallon-Baudry and Bertrand, 1999.

burst, around 50 to 150 ms, reflects perception of the visual input. The second gamma burst occurs about 250 to 300 ms after stimulus onset and appears with both the real and the illusory triangle but not with control stimuli that do not look like a triangle. The illusory Kanisza triangle in column A of Figure 8.18 has no sides, only three white pointed wedges against three dark disks. But subjects still perceive the illusory triangle as real. Thus, the second gamma burst signals a *perceived* triangle. It does not occur when a pseudo-triangle is presented (lower graph). The moment of recognition of the triangle can be considered as a match between the visual input and a memory. It is the visual cortex saying, *'There it is'!* in response to the visual triangle.

As you can see from the top of column C, the second gamma burst is located over the subject's early visual cortex. Because visual areas have two-way connections, it is likely that higher-level visual regions may also be oscillating in synchrony with the occipital cortex (area V1). As we will see, one likely function of gamma activity is to synchronize multiple visual maps.

A series of iEEG studies over the past decade have demonstrated that gamma bursts (and other frequencies) occur in close association with cognitive tasks. They are an important part of the signaling mechanism underlying neural information processing. Because that has been a contentious subject in previous years, the new evidence (along with novel EEG

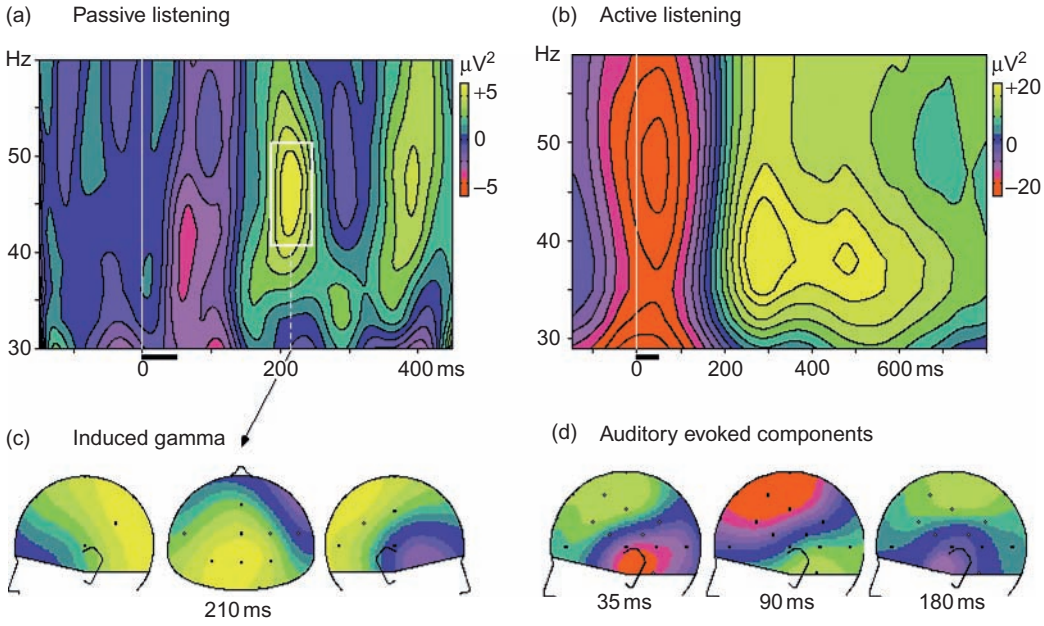

FIGURE 8.19 Gamma activity in listening. Auditory perception shows striking gamma band bursts in intracranial EEG (a), markedly stronger in the 'active listening' condition (b). This condition presumably adds executive attention to the conscious auditory stimulus. The term *induced gamma* (c) refers to endogenous brain activity that occurs with a 210-ms lag after the stimulus onset and may reflect reentrant activity between multiple levels of analysis (such as acoustics, speech phonemes, syllables, or morphemes and words). *Source*: Tallon-Baudry and Bertrand, 1999.

and MEG findings) is very important. Notice that measuring fast oscillations with fMRI is more difficult because of the five-second rise time of the blood-oxygen level (BOLD) response. Yet fMRI has its own great advantages, and converging studies of fMRI and electromagnetic brain signals have become very important.

Figure 8.19 extends these findings to hearing. On the left side, passive listening results in induced gamma (about 200 ms after stimulus onset). On the right graph, the duration and frequency spread of the gamma activity are longer and more widespread in 'active listening', a more attention-demanding way of listening. There are now many findings showing that active executive attention enhances gamma activity, as we will see. There is a great deal of psychological evidence showing that active listening improves stimulus processing and learning.

Notice that these iEEG were published in the past decade. They represent a marked advance in our understanding of high-frequency events in the brain. While animal studies with implanted electrodes have been used for many years, these human studies have served to confirm and extend their findings to human cognition. Implanted iEEG in humans has much better spatial sensitivity than surface EEG, as well as better sensitivity and signal-to-noise ratio. A higher range of frequencies can also be recorded. Together with non-invasive brain imaging methods, these kinds of data are having a very great impact on our understanding of the brain in human cognition.

2.9 Gamma synchrony may bind visual features into conscious objects

So far, we have seen two kinds of evidence for gamma in cognition: gamma amplitude and gamma synchrony. Amplitude is the loudness of the rock band; synchrony is the degree to which everybody plays in rhythm. It is likely that the two go together. However, by high-temporal-resolution recording, gamma synchrony can be separated from gamma amplitude.

One possible role of gamma synchrony is to 'bind' or integrate separate stimulus features into meaningful objects (see Figures 8.12 and 8.13). Different visual regions represent different features, and at some point the brain needs to bring them together into a single object. That may also be the point at which visual information becomes conscious.

The object recognition area of the macaque brain has been shown to differentiate between conscious and

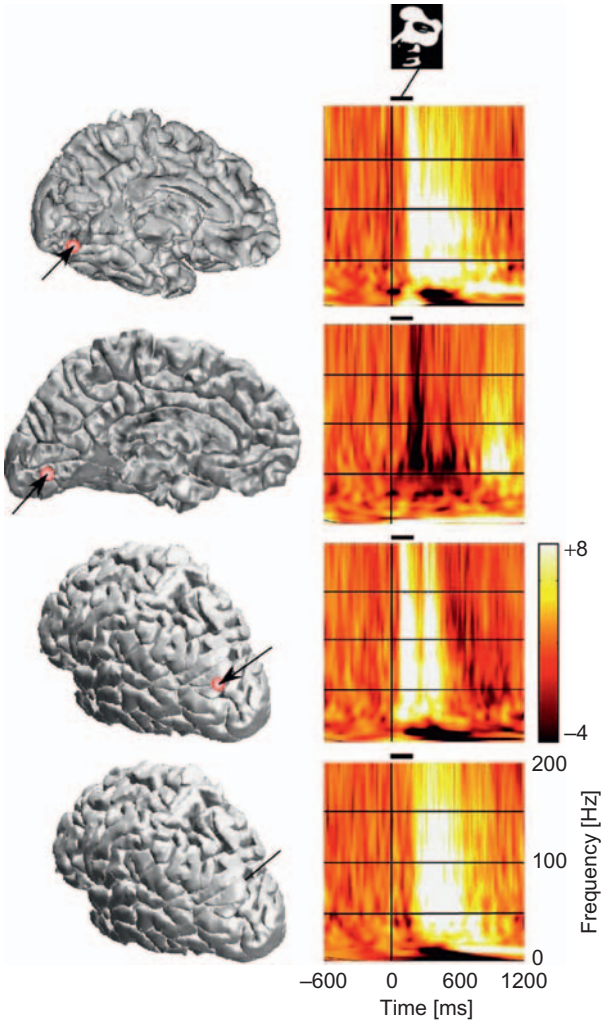

FIGURE 8.20 Face perception involves gamma activity in multiple visual maps. Lachaux *et al.* (2005) used iEEG to record during face perception directly from four different visuotopic regions in the human cortex. The stimulus was a 'Mooney face' (top), which takes some time to recognize as a human face. Three of the four regions show a fast, intense gamma band burst beginning <100 ms after stimulus onset (from the top, fusiform gyrus, area V1, lateral occipital gyrus [BA19], and left intraparietal sulcus). The fourth, area V1, actually shows a decrease in gamma for about 700 ms (dark area), followed by a high gamma burst. The authors conclude that the gamma band response can be different in different brain regions. These differences may be due to selective inhibition in different visuotopic maps. Inhibitory neurons are believed to be constantly shaping the massive activity of excitatory pyramidal cells in cortex. The late gamma burst in V1 may reflect top-down activation from the face recognition area (fusiform gyrus). *Source:* Lachaux *et al.*, 2005.

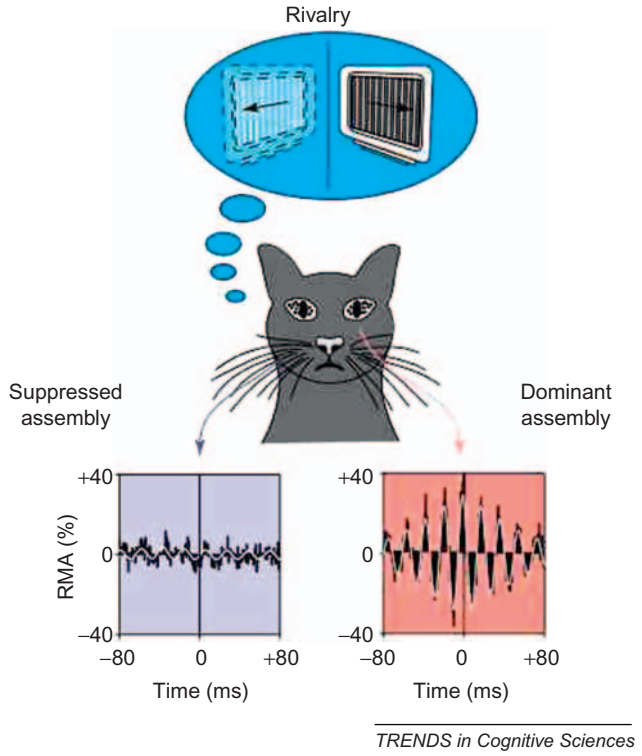

FIGURE 8.21 Conscious feature integration by gamma synchrony. Is feature integration required for conscious object perception? Many scientists have argued for this position. Engel and Singer published a classical experiment in which the 'dominant assembly' of neurons could be attributed separately to the left or right eye. Left or right visual dominance columns in cat cortex were monitored directly, using binocular rivalry for motion. A drifting grating moved in opposite directions in the two visual fields, providing two competing inputs that could not be fused into a single, coherent percept. Gamma activity synchronized only in the dominant visual field, which the cat was trained to match with an unambiguous stimulus, thereby signaling the conscious stimulus. *Source*: Engel and Singer, 2001.

unconscious visual input. When we see a face, many visual feature maps in the brain show gamma activity (Figure 8.20). Conscious objects combine multiple features; in a normal visual scene we do not see floating points of light or points of color or contrast edges. But we can see visual objects as distinct conscious experiences.

Figure 8.20 does not directly show synchrony but only amplitude in the gamma range. One of the early experiments to demonstrate gamma synchrony between brain areas in conscious vision was published by Engel and Singer (Figure 8.21).

Engel and Singer studied binocular rivalry in the cat (see Chapter 6), a classic paradigm that allows us to compare conscious versus unconscious stimulus processing in the visual brain with identical physical input to the two eyes. They recorded directly from ocular dominance columns in visual cortex, which distinguish between the input from the right and left eye. Experimental cats were surgically altered to have nonoverlapping visual fields, a condition called strabismus or 'lazy eye' when it happens naturally.

Strabismus leads to one-sided ocular dominance in the visual cortex, determining which eye will dominate vision; that is, which eye 'is conscious'. In this case, when the rivaling stimulus became conscious in the right versus left eye, the dominant cortical field could be recorded separately for each eye.

Engel and Singer (2001) showed two opposing streams of moving grids to each of the cat's eyes, a kind of binocular rivalry that cannot be fused into a single, conscious visual experience. The results are shown in Figure 8.21. Notice that in the cat's cortex, the dominant (conscious) eye demonstrated gamma synchrony locked to the 'conscious eye', whereas the nondominant (unconscious) eye showed no synchrony. The cat was asked, in effect, what it saw, by stimulus-matching to an unambiguous drifting grating, as if the experimenters were asking, 'Are you seeing this one or the other one'? Thus, the cat was able to provide a 'voluntary report' on the conscious stimulus. Similar experiments have been extensively performed in macaques, with comparable results.

Notice that the peak level of activity in Figure 8.21 occurs with perfect synchrony at time t = 0 in the dominant assembly of neural populations. A smaller peak occurred at time t = +/− 20 ms and at time multiples of 20 ms. These peaks fall off as the visuotopical neural maps drift away from perfect synchrony. Nevertheless, even the smaller peaks occur at 20 ms intervals, suggesting that gamma synchrony is occurring at 50 Hz – that is, one cycle per 20 ms. In contrast to the dominant neural assembly, the suppressed assembly shows little or no synchrony. This was also the stimulus that the cat could not match to the sample stimulus, as if it were telling us that there was 'nothing to see' in the nondominant eye.

The Engel-Singer type of experiment involves an historic advance in our understanding of conscious vision in other mammals. Similar experiments have been performed in humans as well, as discussed in Chapter 6.

A very different kind of method provides converging evidence for the role of brain rhythms in conscious vision. Figure 8.22 shows a recent finding using transcranial electrical brain stimulation, specifically a technique using an alternating-current (AC) field. The graph is a traditional psychophysical curve, relating a physical stimulus to a subjective experience. In this case, the conscious experiences were 'phospenes', visual 'flashes' that can be evoked by direct brain stimulation. Phosphenes were first demonstrated in humans by the pioneering neurosurgeon Wilder Penfield and colleagues some 50 years ago during presurgical exploratory studies of intractable epilepsy patients (Penfield & Roberts, 1959). However, the conditions for reliable phosphenes have not been well understood until recently. Because

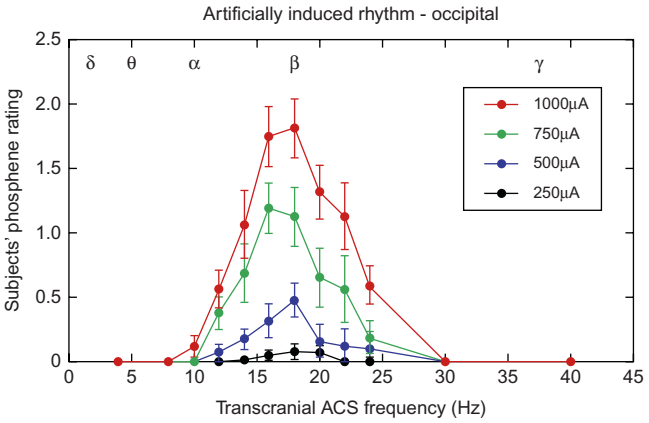

FIGURE 8.22 Transcranial stimulation can evoke conscious 'flashes'. Conscious phosphenes (visual flashes) can be evoked across the scalp by transcranial Alternating Current Stimulation (tACS) over the occipital cortex. Kanai *et al*. (2008) used tACS to sample the frequency spectrum from 3 to 30 Hz and obtained these elegant psychophysical curves relating tACS frequency to subjective visual sensations. The curve peaks just below 20 Hz in the beta range, suggesting that intrinsic rhythms were induced by the electrical field. *Source*: Kanai *et al*., 2008.

they are subjective experiences (unlike other types of direct stimulation of the visual cortex), they clearly tell us something about visual consciousness.

A recent study by Kanai *et al*. (2008; Figure 8.22) shows reliable phosphenes evoked by alternating current in the beta range (~20 Hz, sometimes called low gamma). This finding is again quite historic. The psychophysical function obtained by Kanai *et al*. demonstrated how regular these phenomena now appear to be. This is significant, because phosphenes long have been considered to be difficult to evoke in a replicable way. The consistent peak just below 20 Hz is also remarkable and suggests that conscious visual events require rhythmic brain events, as we would expect from the iEEG experiments just presented. Notice that the peak subjective rating rises predictably as the current level is increased (in micro-amperes at the scalp).

If the evidence presented so far makes the case for gamma synchrony as one ingredient of common cognitive tasks, how does gamma synchrony 'run' a complex task? After all, perceiving a face or a word takes a lot of processing. It is performed very fast, and one component of the task needs to rapidly lead to the following one. Independent evidence suggests, for example, that the purely sensory aspect of perception may occur before the analysis of meaning, at least in language perception. The next experiments shows how successive spurts of gamma synchrony may enable different phases of a single cognitive task.

Again, robust evidence has been found in exploratory studies of conscious epileptic patients using iEEG

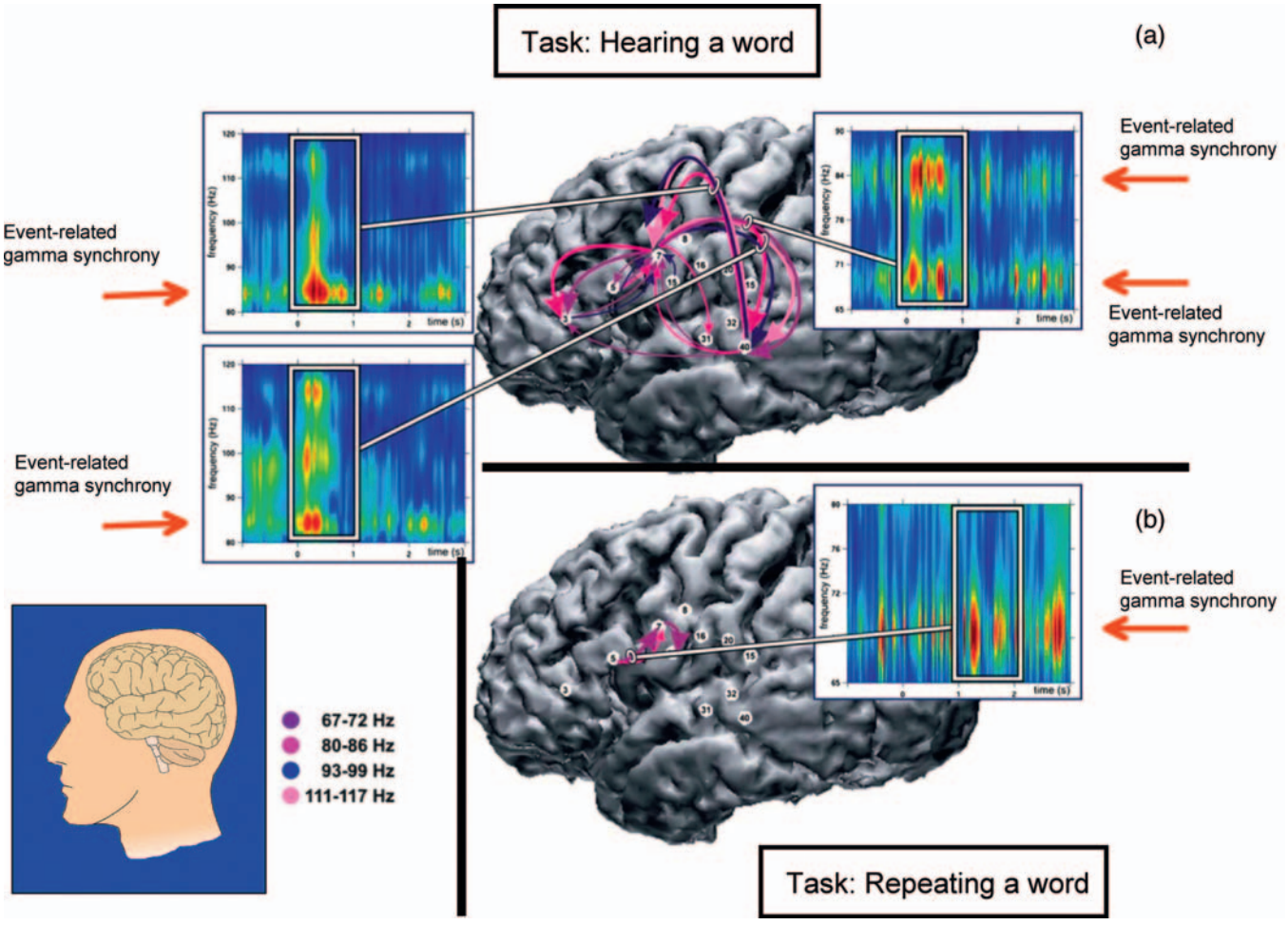

FIGURE 8.23 Multiple synchronous gamma bursts in speaking and hearing. Crone *et al*. (2006) studied conscious epileptic patients with implanted cranial electrodes. The results suggest that the brain is triggering synchronous gamma bursts between different brain regions involved in hearing, speech perception, and speech production. Each phase of the name repetition task seems to evoke a separate synchronous gamma burst in somewhat different regions of the left hemisphere in a single patient. Gamma synchrony was observed in four parts of the high gamma band, ranging from 57 to 117 Hz (see pink, blue, and purple arrows). Red horizontal arrows point to gamma synchrony observed in specific parts of the frequency range. In the graphs, red colors indicate highest amplitude, with yellow and light blue colors representing lower amplitudes. The graphs show frequency on the vertical axis and time before and after the stimulus in hundreds of milliseconds on the horizontal axis. *Source*: Adapted from Crone *et al*., 2006.

to localize the epileptic source and to identify those brain regions whose damage during surgery would affect essential functions like vision, audition, and language. Crone *et al.* (2006) demonstrated that gamma synchrony between local regions of the left hemisphere is often *transient*, indicating a brief period of coordination between two parts of the brain. In Figure 8.23, a patient with a grid of electrodes over the left hemisphere showed event-related gamma synchrony, with brain rhythms triggered by a simple picture naming task. The patient was given a series of spoken words and asked to keep each one in memory and then repeat it on cue. In this way, auditory input and the naming response could be kept separated in time. The purple colors in the figure show different bands in the high gamma range (67–117 Hz) in different parts of the left hemisphere. Hearing each word triggered several synchronous gamma bursts over the auditory and speech perception cortex (Wernicke's area). Speaking the same word triggered gamma synchrony over Broca's area, as we might expect. Notice that local cortical patches of the left hemisphere showed synchronous bursts in a complex series, as indicated by the purple, pink, and blue arrows.

So far we have seen local gamma synchrony in local areas of cortex. Long-range gamma synchrony also has been observed, as we will see later, among distant parts of the cortex that must cooperate in carrying out some task.

2.10 Theta rhythms have multiple roles

Gamma rhythms are not the only important oscillations in the brain; for purely historical reasons, gamma has come to mean a wide, high band of oscillations from perhaps 30 to 120 Hz and sometimes higher. This is an accident of scientific history, simply because fast oscillations were more difficult to record at one time, in part because they show up better with implanted electrodes. It is clear, however, that slower rhythms play fundamental roles. The theta rhythm is one of the slowest oscillations in the normal waking state, cycling 4 to 7 Hz, just above the delta rhythm that dominates SWS, and the more recently discovered slow oscillations that may go down to .01 Hz (Figure 8.24).

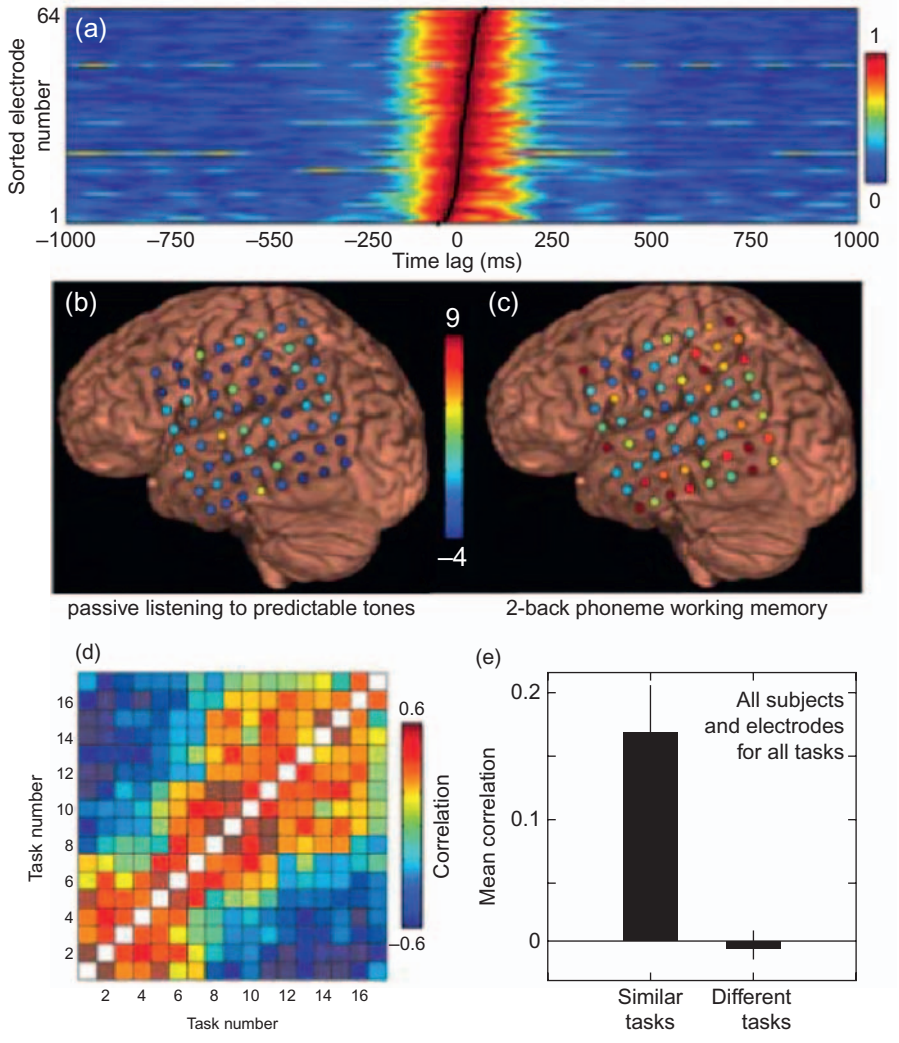

FIGURE 8.24 Theta-gamma multiplexing across 16 different tasks. Theta-gamma phase locking across 16 different tasks, using intracranial EEG (iEEG). (a) Shows an index of phase locking (t = 0 indicates precise phase locking, with less correlation as the time lag increases in either direction). The left lateral hemispheres shown for Subject 2 show colored dots for electrode locations corresponding to the color bar in the center of (b) and (c). Notice that passive listening to predictable tones shows theta-gamma locking (d), but, as shown in (c), a difficult working memory task, reporting two phonemes back from the current phoneme, has more yellow and red colors, indicate increased phase locking in the more demanding task. (d) Shows 16 tasks, with the highest correlations (red) for squares nearest the diagonal, which are the most similar to each other. The same point is made in (e), indicating low but significant correlations in phase locking between similar tasks compared with dissimilar ones. *Source*: Canolty *et al.*, 2006.

Theta seems to 'carry' gamma oscillations in much the way an AM radio frequency carries a voice signal. Theta is believed to play a key role in episodic memory and frontal lobe activities. Theta is one of the basic carrier frequencies of the hippocampus, observable during both episodic memory encoding and recall. Theta is believed to enable the coding and decoding of hippocampal learning in the neocortex, especially the frontal lobes. In the surface EEG, it can be observed along the midline of the scalp when episodic memories are recalled and during executive tasks that engage both the lateral and medial frontal lobes.

There are many ways for brain waves to interact: like water waves, they can add on to each other or cancel each other. Frequency modulation is also possible, allowing for speeding and slowing of waves. What's more, there is evidence for phase modulation, so that the degree of phase locking between two sources of gamma might shift in order to pass some signal. Phase modulation has been proposed as a mechanism for hippocampal coding of place memory in rats.

There is no reason to suppose that the brain has only one or two kinds of population codes. The nature of neural coding is a hot scientific question, and it is by no means settled.

We have seen that theta oscillations may group gamma, and in some conditions alpha may group gamma activity as well. Steriade (2006) has suggested that slow oscillations may generally work to group faster ones. Even the newly discovered 'slow oscillations' that range from 0.1 to the delta range may serve to group theta, alpha, beta, and gamma.

2.11 Alpha rhythms

In 1929, a German psychiatrist named Hans Berger made the first observation of human EEG by placing an electrode on his young son's head just above the occipital cortex. The key to Berger's discovery was a new, powerful amplifier that could amplify the small electrical voltages on the surface of the head and convert them into visible deviations of an ink pen, writing traces on a moving strip of paper. Berger asked his son to open and close his eyes and found that with eyes closed, a small sinusoidal wave could be picked up. Berger called it the *alpha wave* (Figure 8.25). (The names alpha, beta, and gamma, etc., are largely historical accidents.) Alpha waves conventionally are defined to oscillate from 8 and 12 Hz (Hertz = cycles per second). The size of alpha has been found to be increased by internal tasks, such as mental calculation and working memory. Recent theory suggests that alpha reflects the selective suppression of task-irrelevant areas and activities in the brain (Palva and Palva, 2007).

In retrospect, Berger's discovery was a historic moment in brain science and medicine. But until the last few decades, the surface EEG was difficult to analyze. Even today, scalp EEG poses practical difficulties. For example, we still have no foolproof way of locating the sources of the surface potentials. That problem can be solved with other techniques, however, including intracranial EEG, MEG, PET, and fMRI. Surface EEG has important practical applications in medicine. It is by far the easiest and least expensive brain recording method, and it continues to be useful. There are constant efforts to improve its accuracy.

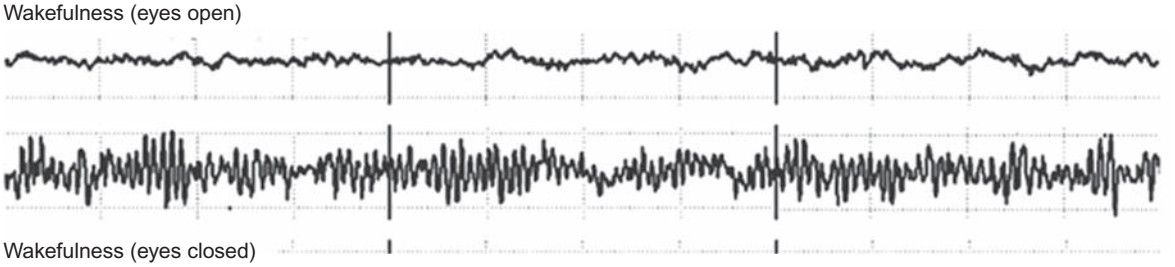

FIGURE 8.25 Alpha waves with eyes open and closed. The raw EEG over the occipital cortex, showing irregular waking activity with the eyes open (upper trace) and spontaneous alpha waves with eyes closed (lower trace). A great deal of research has been conducted since Berger's 1929 discovery of these phenomena, but they are still something of a puzzle. One major question is what occurs to irregular waking EEG when the eyes are closed, and alpha 'idling' appears instead. Alpha is then presumably actively suppressed, just as complex, waking EEG appears to be suppressed when alpha appears in the raw, unanalyzed EEG. *Source*: Tononi in Laureys & Tononi, 2009.

The brain is full of criss-crossing electromagnetic waves. What is remarkable about Berger's eyes-closed alpha waves is that they are so simple. Visible alpha is remarkably regular, easily observable, and related to cognitive events. The traditional explanation is that the brain is in an 'idling mode'.

Berger's next finding was called 'alpha *blocking*', and it is also straightforward. When subjects generate regular alpha waves they will be interrupted when they open their eyes or perform active thinking or imagery. Instead of regular sine-like waves, the EEG over the occipital cortex shows irregular, fast, and low-voltage waves (see Figure 8.4). These fast waves were called *beta* (13–30 Hz) and *gamma waves* (30 Hz and higher). The beta-gamma signal is a useful sign of conscious waking activity. It is routinely used for medical diagnosis. Keep in mind, however, that the visible EEG waves are just the waves on top of the oscillatory lake. Underneath the irregular scalp EEG there are known to be synchronized rhythms. They can be found by mathematical analysis and by recording with deep-brain electrodes. It therefore seemed as if there were two kinds of EEG signals: alpha waves, sometimes considered to reflect 'mental idling', and active thinking, marked by complex, fast, and irregular brain activity. Considering the complexity of the brain, these early observations were surprisingly simple and lasting.

Sinusoidal waves are very common in nature. They can be observed when any rotating source sends out a signal over time. If you attach a small light to the rim of a bicycle wheel and ride the bike in a straight line at night, the light will trace out a sine wave. The mathematician Joseph Fourier (1768–1830) proved that any complex wave can be analyzed into a set of sine waves, a process that is called Fourier analysis. Modern EEG is routinely run through high-speed Fourier analysis, so that we can see the sine-wave components of complex brain activity. In practice, we often tend to group wave components into *bands,* using the conventional ranges, like 4 to 7 Hz for theta, 8 to 12 Hz for alpha, and so on. However, it is important to bear in mind that nature may not always go along with our conventions. Different subbands of gamma routinely seem to do different tasks, for example.

Recent studies show that alpha can be found during mental imagery and other mental activities (Figure 8.26). Like other slow rhythms, alpha may also group faster activities. Intracranial EEG recordings show both alpha synchrony and desynchrony. (Desynchrony is similar to Berger's observation of 'alpha blocking'.)

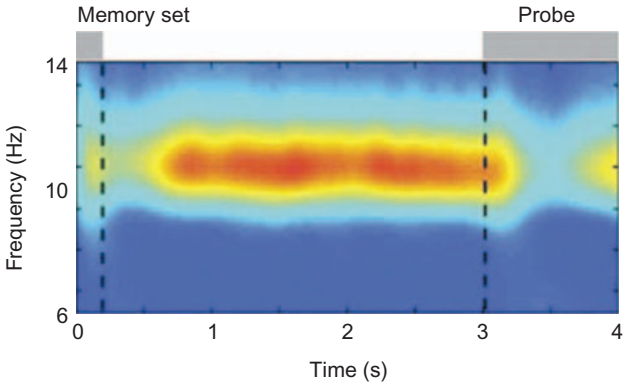

FIGURE 8.26 Alpha may group gamma oscillations in working memory. In an immediate memory task, Palva and Palva (2007) showed a strong burst of alpha activity (the horizontal red and yellow bar) for three seconds while subjects hold a number in memory. Notice that the most intense activity is consistently centered near 12 Hz. *Source*: Palva and Palva, 2007.

We are only beginning to understand neural coding in the brain. It is important to keep in mind that both synchrony *and* its absence may convey information, in much the way that both the presence and the absence of light reveals visual information – patterns of shadows are as useful as patterns of light. Signaling codes use both signals and the absence of signals, as in Morse code.

Palva and Palva (2007) suggest that cross-frequency phase synchrony between alpha, beta, and gamma oscillations 'coordinates the selection and maintenance of neuronal object representations during working memory, perception, and consciousness'. In some experimental conditions both alpha synchrony *and* desynchrony can be observed.

Figure 8.26 is a clear demonstration of the involvement of alpha activity while holding items in working memory. As mentioned previously, it is likely that this increase in alpha activity may also be multiplexed with other waveforms. But the evidence suggests that alpha plays a functional role in human cognition and that it does not represent only an 'idling rhythm', as many scientists believed until recently.

3.0 ATTENTION ENHANCES PERCEPTION, COGNITION, AND LEARNING

Common sense makes a distinction between *attention* and *consciousness*. The word *attention* seems to imply the ability to direct cognitive resources to some event.

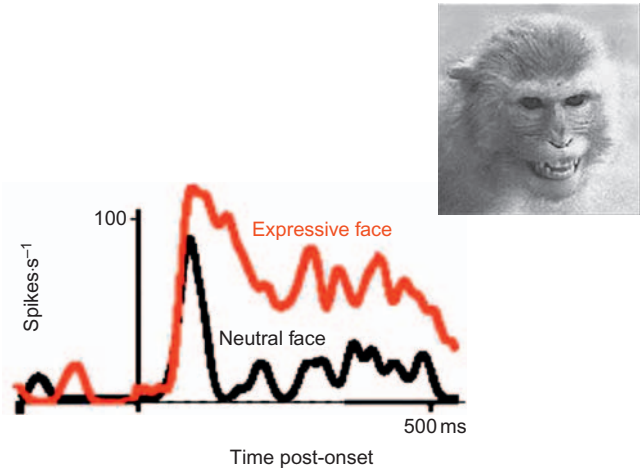

FIGURE 8.27 Bottom-up attention: A monkey threat face. Visual face-sensitive neurons fire faster when macaques see a threat face, as in the photo, compared with a neutral face. A threat face is a biologically important signal. The graph shows spikes per second in a neuron located in the visual face area, the fusiform gyrus. The threat firing rate is shown in red and the neutral rate, in black. *Sources*: *Top*, Parr and Heintz, 2008; *bottom*, Vuilleumier, 2005.

If you can't remember a technical term in this book, for example, you might try to clear your mind of other thoughts and 'pay more attention' to trying to remember the word. The word *attention* has a kind of 'pointing' or 'directive' sense. But in everyday language, 'consciousness' refers to an experience – of reading this sentence, for example, or of having thoughts, feelings, and images that may come up after reading *these words*. Selective attention implies a choice among possible events. Consciousness seems to be the experience of an event *after* it has been selected.

We can often decide what to become conscious of: whether to continue reading this book, turn on the television, stop thinking about a friend, and so on. There is also automatic attentional selection if stimuli are intense, dynamic, or biologically or personally important (Hahn *et al*., 2006). We constantly scan the world, even without intending to do so, and often pick up significant events automatically.

Like most mammals, monkeys can be fierce fighters. When facing a threatening snake or competitor they tend to send out warnings first, using threat faces, screams, and behavioral displays. Figure 8.27 shows a 'bared teeth' threat face made by a macaque. Monkeys and humans show increased responding in visual face neurons to threat faces. They are biologically vital. For that reason, threat faces are likely to be processed 'bottom up', much as we expect alarm bells to be processed bottom up: This important stimulus interrupts the flow of other experiences.

Young mammals can tell the difference between 'pretend' aggression and the real thing. Play aggression is part of 'rough and tumble play', something that young mammals often like. Lin *et al*. (2009) have shown that attention to threat faces can occur unconsciously, although the *outcome* of that attentional process is usually conscious.

3.1 The Posner flanker task

Posner and colleagues have devised a simple probe for visual attention called the flanker task. They asked subjects to pay attention to a stimulus at a known location on the right or left side of the fixation point (marked with a dot or a plus sign). Because humans have a very limited foveal 'keyhole' through which we fixate a small part of the visual field at any single moment, it is possible to control the exact information that is available to a subject. (We see only about 3–6 degrees of visual arc when the eyes are fixed on a point. Try it!)

The flanker task allows for testing of both voluntary and nonvoluntary attention, by giving subjects either correct or incorrect information about the flank on which the target stimulus will appear (Figure 8.28). This can be varied from trial to trial. By mixing correct and incorrect cues before a stimulus, data can be collected in a single experiment on expectation-driven (correctly cued) and unexpected (incorrectly cued) flankers. The task is simple enough to administer in an fMRI scanner in a half hour or so, and the resulting brain scans provide separate information about expectation-driven trials and unexpected trials. By subtracting the 'unexpected attention' brain activity from the 'expected attention' scans, Posner and coworkers were able to obtain a relatively pure measure of the brain regions involved in voluntary visual attention.

Because the flanker task is the most common method for studying visual attention, we will go through it in some detail. The flanker task is simple, effective, and adaptable. For example, the target stimuli can be emotional faces, allowing us to explore how the brain pays attention to emotional events (Fan *et al*., 2002; Posner and Petersen, 1990).

Here is how the flanker task works:

1 Subjects keep their gaze on the fixation point. They look at the target from a known distance so that the degree of visual arc subtended by the fixation

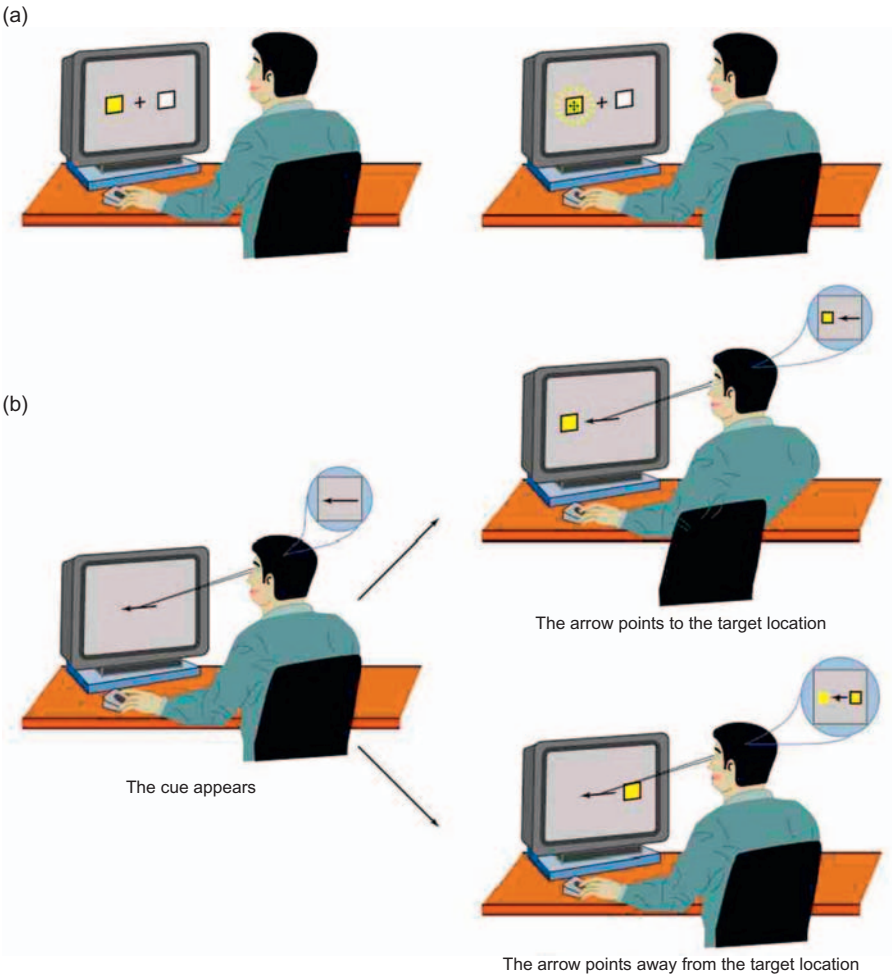

FIGURE 8.28 The flanker task for assessing attention. The flanker task is used to study visual selective attention and its brain basis. The subject looks only at the fixation point. Directional cues like the arrow draw attention to left or right flank, but no eye movements are allowed. Accuracy and response speed measure costs and benefits, depending on whether the flanker was cued or counter-cued. Targets presented on the unexpected side have a cost in time and accuracy and are believed to reflect the ability to override cued attentional set. *Source*: Reynolds *et al*., 2003.

point is always the same. The fovea (the highest-density region of the retina) is kept focused on the fixation points, and data from trials with eye movements away from the fixation points typically are discarded. Outside of the fovea, which covers only 2 to 4 degrees of arc, the retina loses resolution and is sensitive only to light and dark edges. (It follows that our normal sense of a rich and colorful visual world is a construction of the visual brain, not a literal record of the input into the retina.)

2 When flanking stimuli appear on the right or left side of the fixation point, they can be detected using only covert attention, because the eyes are kept fixed on the crosshairs. Posner and Petersen (1990) discovered that people can selectively increase the attentional processing efficiency of retinal inputs that are a few degrees off the fovea (see Chapter 6).

3 Subjects may be cued by an arrow pointing left or right to expect a target to flash briefly to the right or left of the crosshairs, or a momentary brightening of the left flanker box tells the subject that the target will soon flash on the left side with 80% probability.

4 In the figure, the target is flashed in the expected location for a fraction of a second. Subjects respond as quickly as possible. When their cued expectations are correct, their reaction times and accuracy are optimal.

5 However, the target might also be flashed to the other flank, in the unexpected location. This unexpected event imposes a cost in reaction time and accuracy.

Thus, attention has both benefits and costs. An increase in speed and accuracy at the expected location compared with an unexpected location is considered to be a *benefit* of attention. A loss of speed and accuracy for the unexpected stimulus is considered to be the *cost* of the failing to pay attention to that event. The flanker task therefore permits quantitative assessment of the cost-benefit tradeoffs in terms of speed and accuracy.

The ANT task (Fan *et al*., 2002) is a generalized version of the flanker task, to allow testing of three separable aspects of attention: alerting before an expected signal (after an 'alert' cue), orienting to a specific location in space (using an arrow to point to the coming flanker stimulus), and executive attention, to act *against* expectations set up by the task. In this paradigm, 'executive attention' is taken to be the opposite of 'automatically controlled attention'. The Stroop Task is a good example of executive or voluntary attention (Box 8.1).

The ANT task allows each component to occur at a different moment than the others. That fact allows brain images to be recorded for the three different components. Various task manipulations can be used to selectively change alerting, orienting, and executive attention. For example, asking subjects to keep several numbers in memory during the task may degrade executive attention because it makes use of central limited capacity but not automatic attention.

Consider the case of a college student in a lecture room, with many sensory inputs occurring at the same time. The student must be reasonably alert, orient to the desired sensory stream, and allocate attentional

BOX 8.1 Stroop color-naming and executive attention

Equipped with a stopwatch and Fig. 8.29, you can easily replicate Stroop's original demonstration (Stroop, 1935). For columns 1 and 2, the task is to read each list of words aloud as fast as possible, ignoring their print color. Begin by covering all of the columns except column 1. Start the timer when you say the first word and stop it when you say the last word. Record your time. Now cover all columns except column 2 and read the words aloud again. For columns 3 and 4, the task is changed to naming the print colors aloud as fast as possible, ignoring the letters or words. Do this for the rows of colored letters in column 3 and then for the rows of colored words in column 4.

Stroop observed three primary results. First, reading words was faster than naming colors. This is consistent with word reading being more practiced and hence more automatic than color naming (Cattell, 1886, and Fraisse, 1969). Second, there was little difference in reading the words in columns 1 and 2 (Stroop's Experiment 1): mismatched ink colors did not produce interference in reading the words. Third, in sharp contrast, switching from nonwords to words in color naming made a very large difference between columns 3 and 4 (Stroop's Experiment 2): naming the colors of incompatible color words showed dramatic interference. Apparently, the greater automaticity of word reading leads to the words being read even though they should not be, producing conflicting responses to each stimulus. This both slows down color naming responses and makes errors – reading words instead of naming colors – more likely.

1	2	3	4
red	blue	xxx	green
green	green	mmmmmm	blue
yellow	red	hhhh	yellow
red	blue	sssss	green
blue	yellow	hhhh	red
green	blue	xxx	blue
blue	green	sssss	yellow
red	red	xxx	xxx
yellow	yellow	mmmmmm	green
blue	green	sssss	red
yellow	yellow	mmmmmm	blue
green	red	hhhh	yellow
Time			

FIGURE 8.29 The Stroop task.

Modern versions of the Stroop task are typically computer-controlled displays of a single word in color, rather than multiple items on a card, permitting more control and more precise measurement of individual item and sequence effects. Also, although Stroop did not include a congruent condition (RED printed in red; say 'red'), modern versions of the task often do. Both of these modifications were introduced by Dalrymple-Alford and Budayr (Dalrymple-Alford & Budayr, 1966).

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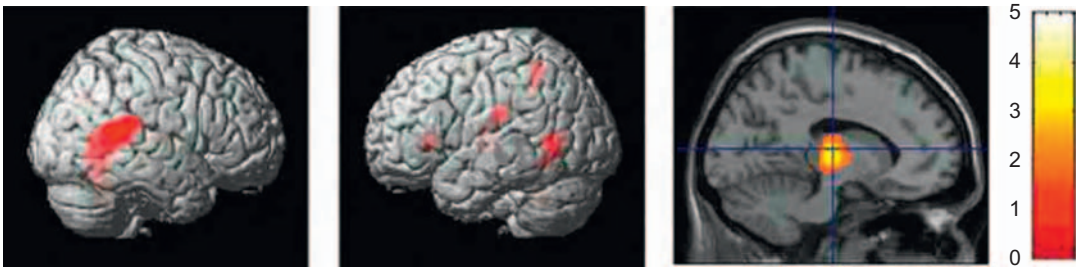


FIGURE 8.30 Posner attentional control network. Using the flanker task, Posner and colleagues demonstrated activation of a network of brain regions for executive attention. The image on the right shows high thalamic activation, probably involving the pulvinar and mediodorsal nuclei of the thalamus. See Figure 8.31 for a model using these areas. *Source*: Fan *et al*., 2005.

resources to the task of keeping track of the lecture, taking notes, and the like. Brain areas for alertness are located in right frontal and parietal regions (Witte and Marrocco, 1997). But as we have seen, alertness also requires the waking state, which depends on the brainstem, thalamus, and cortex. Brain areas for orienting are located in right temporoparietal junction (TPJ) and the inferior frontal gyrus (IFG, corresponding to Broca's area in the language hemisphere) (Corbetta *et al*., 2000). Finally, voluntary control of attention involves the anterior cingulate and lateral prefrontal cortex (ACC and L-PFC), the pulvinar nucleus of the thalamus, and the superior colliculus (SC) (Marrocco and Davidson, 1998). (See Figure 8.30.) All of these regions have visuotopical maps of one kind or another.

We do not want to confuse selective attention with eye movements, which *also* enhance the quality of visual input. Posner and Petersen (1990) discovered that attentional shifts can be accomplished while keeping the eyes fixed on a single point. That is, we can enhance processing a few degrees to the right or left of our visual fixation point, even without moving our eyes. Visual attention experiments routinely use such implicit attention conditions.

Visuotopic neurons respond to optical stimuli at different levels of analysis (see Chapter 6; Figure 8.31; Itti and Koch). Figure 8.31 gives us a convenient overview. Each layer of the pictured model by Itti and Koch responds to a particular feature of the stimulus: color, line orientation, contrast, and object identity. This is a simplification of the visual brain, which is far more complex and flexible and which must deal with complications such as the constant motion of the eyes and the head, the very narrow limits on foveal vision, and much more. But Figure 8.31 helps to clarify our question.

Each visuotopic map is a two-dimensional mosaic of neurons with rather narrow receptive fields (see Chapter 6). We can therefore ask a more focused question: does attention to some event or to some location enhance signal processing in the appropriate map and the correct receptive field? If the watcher in Figure 8.31 is hot and thirsty while wandering in the Sahara Desert, will his or her attentional system enhance visual processing for ice-cold mugs of beer located on the left side of his visual field? This question is much more specific and testable.

3.2 A model of attention

Itti and Koch (2002) developed a useful model of attention that combines a number of important features. It shows a simplified layered concept of the visual system, with multiple topographic visual maps. The visual maps show line orientation, stimulus intensity (contrast), color, and salience. 'Salience' is defined in terms of feature contrast in any visual map. In light-sensitive regions, it is the contrast between light and dark patches on the map. In motion-sensitive areas like area MT, it may be a stable object against the background of a waterfall. A combined salience map may combine all the contrasting features of multiple visual arrays into a single overall saliency map, one that reflects the unusual, unexpected, or noteworthy features of a visual scene at any level of analysis. A 'Winner-Take-All' (WTA) computation selects the most salient location on a combined map and inhibits competing locations. Obviously, salience can be important to know, but it can also be misleading; for example, when you are watching a visually exciting music video that contains a variety of attention-driving features, you may want to think about something

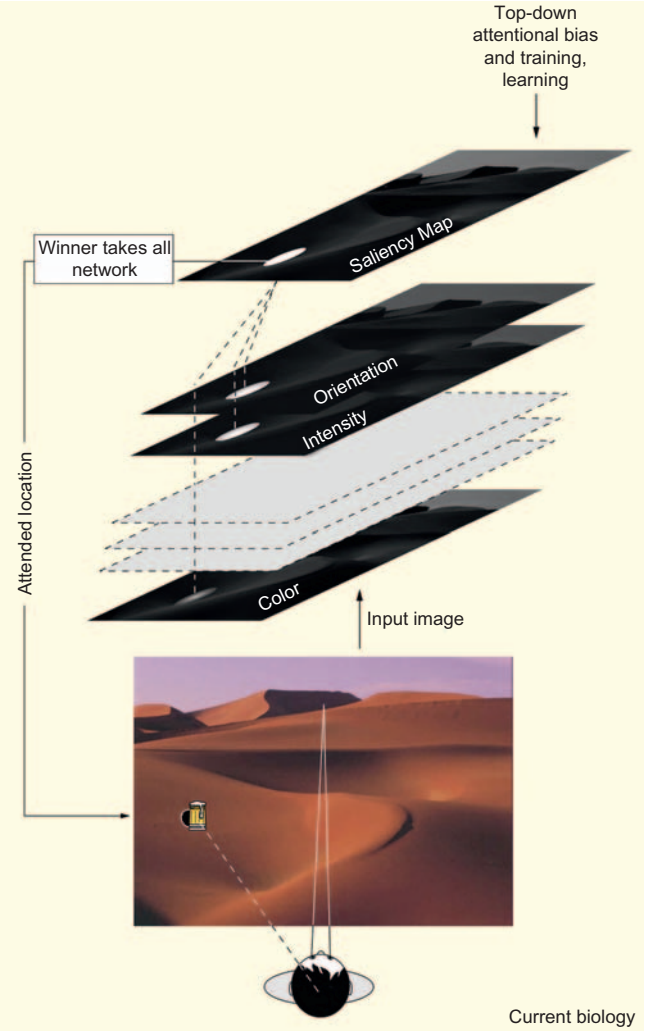


FIGURE 8.31 Multiple visuotopic maps, salience and learning. Multiple visuotopic maps support our conscious experiences of beer mugs and deserts. Notice that the person at the bottom seems to be looking for a cold drink on a hot day in the Sahara. How do our brains select the cold beer? What do we become conscious of? *Source*: Peter Thier *et al.*, (2002); figure adapted from Itti and Koch, 2001.

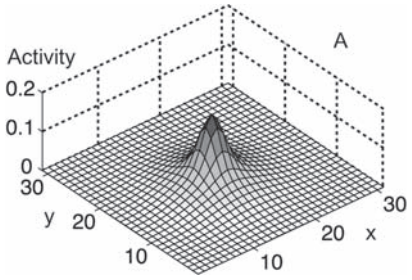


FIGURE 8.32 A Winner-Take-All network. A Winner-Take-All (WTA) network, in which the most activated point in the horizontal plane map inhibits all the surrounding points. The vertical axis is labeled *activity* and may represent a single point in visuotopic space or the summed activity of multiple visuotopic maps. WTA networks are very commonly used in decision-making neural nets, and in the brain both selective attention and conscious perception may make their final 'decisions' using a WTA mechanism. In the case of ambiguous stimuli or dual tasks, like binocular rivalry, the brain makes one of two competing interpretations conscious. One way to model that is to use a WTA network. In the case of ocular dominance columns in the visual cortex (above), we can directly measure a large cortical region that behaves that way when the visual system is provided with different inputs to the two eyes (Section 2.11). *Source*: Standage *et al.*, 2005.

else. You may have to override what is most perceptually salient at any moment.

The concept of a saliency map reflects significance, motivational relevance, and vividness of the input. Many topographical maps in the visual brain are sensitive to motivation and relevance. The man at the bottom of the figure is imagined standing in a hot desert with a cold mug of beer on the far left side of his visual field – just outside of his direct visual field. Selective attention allows significant stimuli like the cold beer to emerge into consciousness. These can be expressed as 'top-down attentional biases' that alter the saliency map on top of the stack. Prior learning also is simplified as an input into the saliency map. All the topographical maps resonate together in synchrony and jointly take decisions in cases where the corresponding points on the majority of maps lead to the same overall result. The output may be an eye movement, allowing the viewer to see the cold beer mug, or it may be a covert shift in attention to the left, again allowing the beer stein to come to visual consciousness. Again, it is possible that the man may want to override the perception of the cold beer on a hot day and focus attention on crossing the desert instead. There are potentially competing decisions in this kind of multilayered network.

An important aspect of the Itti-Koch attention model is the Winner-Take-All (WTA) network (Figure 8.32). WTA networks essentially allow the most active point on the join topographical maps to 'win', with input from saliency, which represents such things as motivation, hunger, and thirst; prior learning about relevance; and so on. WTA is especially important because it also suggests an explanation for conscious experiences of ambiguous inputs, as in the case of ambiguous figures or binocular rivalry. Conscious experiences are marked by internal consistency, even when sensory inputs are not. Most of the words in the English lexicon are highly ambiguous, for example,

but in context (as in this sentence), ambiguous words are consciously experienced in terms of just one interpretation. Thus, a WTA network may be involved in an attentional system, as shown in Figure 8.25, but they are also a very powerful feature of conscious perception. Indeed, we can consider conscious perception to be the outcome of many attentional acts. In reality, there may be no difference in the brain between those two mechanisms.

The common-sense distinction between attention and consciousness suggests that there are attentional control *mechanisms* that often determine what will or will not become conscious. This belief is backed by good evidence.

The term *attention* is used most intuitively when there is a clear voluntary or executive aspect. We ask people to pay attention to things, which implies they can choose to do so or not, depending on some executive decision-making processes. The easiest concept of attention therefore is voluntary selection of information. In human experiments, we invariably ask participants to pay attention to the stimulus conditions of the experiment. Voluntary attention is the kind that is studied most often, and as you might guess from the other chapters, it is likely to use prefrontal cortex in humans (see Chapter 12).

Corbetta *et al*. (2002) recently wrote that voluntary attention, 'is involved in preparing and applying goal-directed (top-down) selection for stimuli and responses'. Automatic attention, on the other hand, 'is not involved in top-down selection. Instead, this system is specialized for the detection of behaviorally relevant stimuli, particularly when they are salient or unexpected'.

While the two systems overlap, they provide a useful first take on the brain basis of selective attention.

However, when we hear a sudden loud noise, our attention is 'captured', even without executive guidance. Attentional capture is an important topic, as we will see in the next section on stimulus-driven attention. As you might expect, visual attention can be captured by human faces, emotional expressions, and bodies, when compared with neutral stimuli. Intense or sudden stimuli, or unexpected events in general, generate larger brain responses than control stimuli. Thus, we can talk about 'bottom-up' capture of selective attention, driven by stimuli, as well as top-down, goal-driven attention, under executive guidance.

In the real world, voluntary and automatic attention are generally mixed. We can train ourselves to pay attention to the sound of the telephone ringing. When it rings and we suddenly pay attention to it, is that voluntary or automatic? Well, it began being voluntary and became more automatic. The dimension of voluntary versus automatic attention is therefore a continuum. Perhaps the strongest case of voluntary attention is the one where we must exert intense mental effort over a period of time (see Box 8.1). A clear example of the opposite pole of the continuum might be a case of a loud sound or a biologically important event like a crying baby, which is hard *not* to pay attention to.

In sum, attention is defined here as the ability to select information for cognitive purposes. Selection may be shaped by emotion, motivation, and salience, and is at least partly under executive control. Thus, selective attention works closely with all the other components of our framework diagram (chapter-opening figure). Without flexible, voluntary access control, human beings could not deal with unexpected emergencies or opportunities. We would be unable to resist automatic tendencies when they became outdated or change attentional habits to take advantage of new opportunities.

On the other hand, without stimulus-driven attention, we would be slow in selecting significant events. We need both voluntary and automatic attention.

As we have seen, specific regions of the brain support functions like sensory perception, working memory, language, and long-term memory. The same is true of selective attention. As techniques have focused on smaller brain areas working at faster speeds, we have learned more about attentional networks and how they select specific kinds of sensory information. Many lines of evidence now agree on some basic facts.

As Figure 8.33 shows, attention is believed to be a selective capacity, either under voluntary control or driven by a stimulus. The result of selective attention is to enhance the quality of the selected information or at least to try to do so. What is the evidence for attentional enhancement?

Voluntary attention in the brain has two aspects, as emphasized by the large yellow arrow in Figure 8.33. Frontal and parietal regions are thought to be involved in *directing* voluntary attention (labeled in blue print); in the case of vision, the *target* regions are thought to be in the visual cortex (labeled in red print). Thus, two questions for a model of attention have to do with (a) the control of selectivity, and (b) the properties of the target that are being attended.

Figure 8.34 shows a current set of hypotheses about specific brain regions involved in voluntary attention to a visual location or stimulus. Notice that voluntary control of attention is attributed to the prefrontal cortex. Top-down activity descends to visual maps related to eye movements (prefrontal eye field, parietal eye

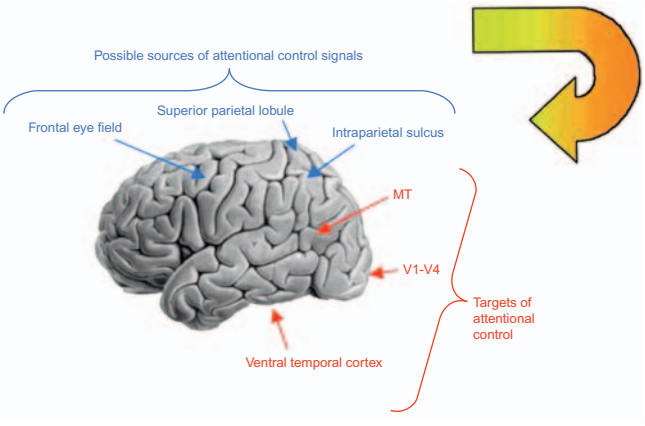


FIGURE 8.33 Voluntary attention: From frontoparietal to sensory cortex. Voluntary attention in perception is directed *to* sensory cortex *by* frontal and parietal regions and perhaps also to other regions of the brain for motor, language, and executive functions. Notice the frontal lobe region, the frontal eye field, which exerts voluntary control over eye movements as well. Parietal regions are believed to be involved in spatially directed attention. Visual regions (in red) are enhanced by attentional mechanisms, such as gamma synchrony among multiple visuotopic maps for the selected spatial location and visual features. *Source*: Yantis *et al*., 2008.

field, and superior colliculus) and visuotopical feature maps (V1-IT). The pulvinar nucleus of the thalamus also contains a visuotopical map, and is hypothesized to bring together saliency cues, basically representing contrasting features and their locations in all the sensory feature maps. Notice that this brain model lacks a WTA mechanism, as postulated by the abstract model shown in Figure 8.32.

Top-down attention is driven by expectations, and in the delay interval (see Figure 8.35A), subjects know where to look, but the stimulus has not yet appeared. Yet visuotopical synchrony still occurs in motion-sensitive areas like MT and the posterior intra-parietal sulcus (pIPS) on the right hemisphere. During this period of attentional expectancy there is significant coupling between MT and IPS. After the delay interval, the stimulus is presented to one side of the visual field so that its first effect will occur in the brain region on the opposite side of the visual stimulus (the contralateral rather than ipsilateral field). In Figure 8.35B, the stimulus presentation time, alpha, and high gamma synchronize regions of the right hemisphere.

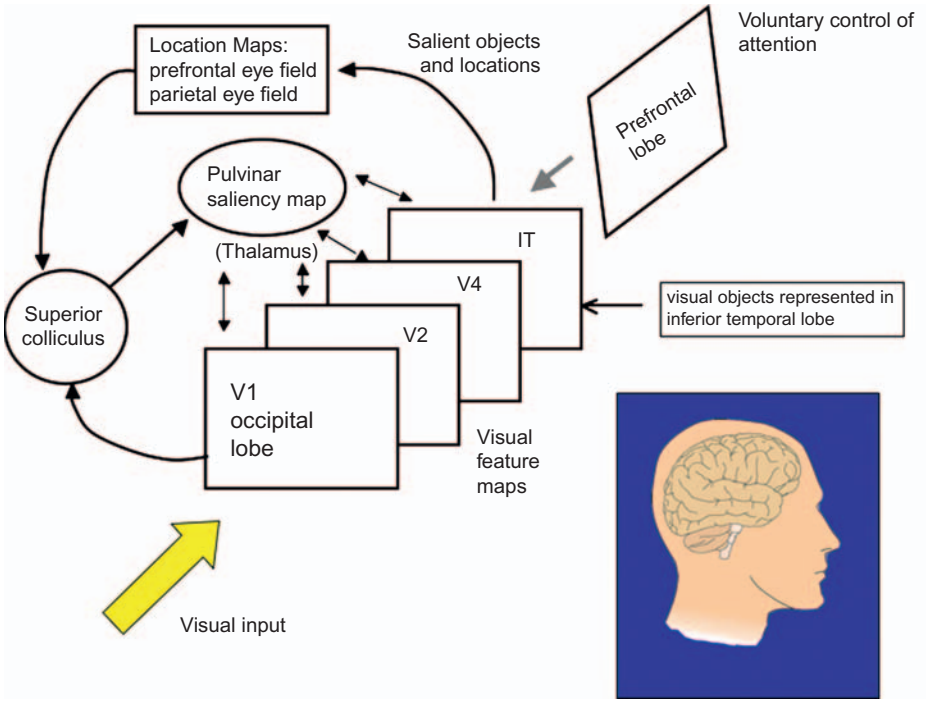


FIGURE 8.34 A brain model for visual attention. Shipp (2005) explores a number of brain models of visual attention. The elements of this model are similar to Figure 8.31, but the components are attributed to specific brain regions. Notice that in addition to cortical maps, two subcortical map-like regions are shown. They are the pulvinar nucleus of the thalamus and the superior colliculus. Many of these same regions are involved in the control of overt eye movements, raising the possibility that in evolution visuospatial attention may have emerged on the prior basis of selective eye movements. *Source*: Adapted from Shipp, 2005.

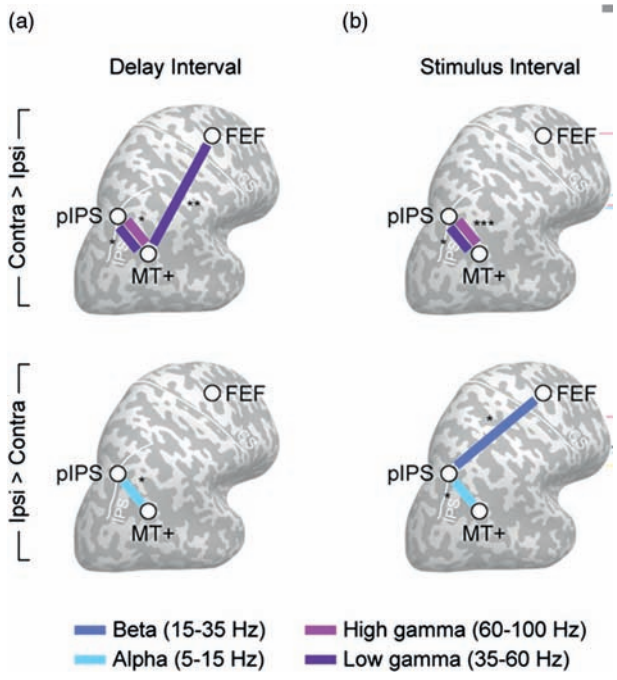


FIGURE 8.35 Synchronizing multiple maps to enhance attention. MEG in a spatially cued motion discrimination task shows high coupling via synchronized alpha, beta, low gamma, and high gamma among four regions of the (right) hemisphere. The right hemispheres have been mathematically 'puffed up' to make cortical areas hidden in sulci (folds) visible. By sending synchronizing signals in different parts of the frequency spectrum, it is possible that the brain can send simultaneous signals that do not interfere with each other. *Source*: Siegel *et al.*, 2008.

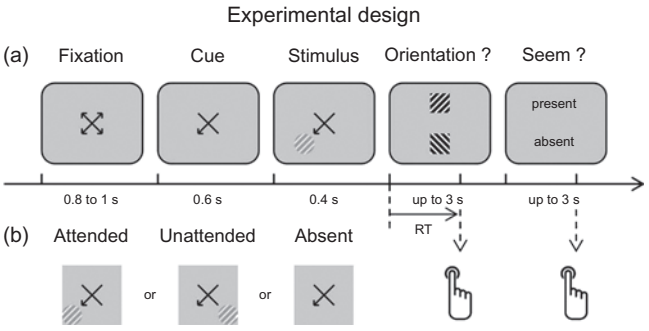


FIGURE 8.36 Separating conscious perception versus visual attention. Wyart and Tallon-Baudry (2008) presented an attentional task (like the flanker task described previously) in which a faint visual grating was presented close to threshold. Eighty-five percent of trials contained a stimulus, about half above and half below threshold. Thus, it would be consciously detectable on about half the trials and undetectable (but still present) on the other half. On half of the stimulus-present trials, subjects were cued where to attend, and in the other half, they were not. Thus, attention was one independent variable (as defined by cued vs. noncued trials), and consciousness of the visual grating the other. Subjects were asked to identify the orientation of the visual grating and its presence or absence. Accuracy rates and reaction times were measured, and MEG was performed. *Source*: Wyart and Tallon-Baudry, 2008.

During the delay period (see Figure 8.35B), anticipatory synchrony occurs prior to stimulus presentation but after subjects have been cued about the spatial location of the expected motion stimulus. In the stimulus interval (see Figure 8.35B), alpha plus low and high gamma can be seen. Notice that FEF, the frontal eye fields, which are involved in voluntary control of attention and eye movements, are decoupled during the stimulus interval. Thus, there is a rich pattern of coupling and decoupling between three important visual attention regions, with four rhythmic bands being synchronized and desynchronized during various periods of the delay and stimulus periods. We could imagine the kinds of signals that might be exchanged between the synchronized brain regions as to enable flexible control of attention (See Figure 8.37).

3.3 Attention versus conscious experiences

Are 'attention' and 'consciousness' two labels for the same thing? That is an ongoing debate. We have taken the position that attentional selection often leads to conscious events and that conscious experiences can influence attention in return. That suggests that conscious experiences and attentional selection can be separated but that they interact with each other. The traditional metaphor is to a spotlight in a darkened theater, in which the theater director can ask for the spotlight to shine on a specific actor or actress. The result of shining the spotlight is to bring out one of the people on stage. By analogy, the spotlight is something that can *select* different players on stage, much as attention selects among a range of possible events. The conscious event corresponds to the appearance of one actor or another in the spotlight. In this view, attention and conscious contents are not identical to each other but are constantly interacting.

A clever experiment by Wyart and Tallon-Baudry allowed for the conscious perception and selective attention to be manipulated separately in the same experiment (2008; Figures 8.36 and 8.37).

It is not known at present whether the same areas in frontoparietal cortex are involved in both consciousness and attention, but there may be some overlap. When selected sensory information becomes conscious, it may activate some of the original frontoparietal loci that selected it in the first place, thus creating a self-sustaining feedback loop for some period of time.

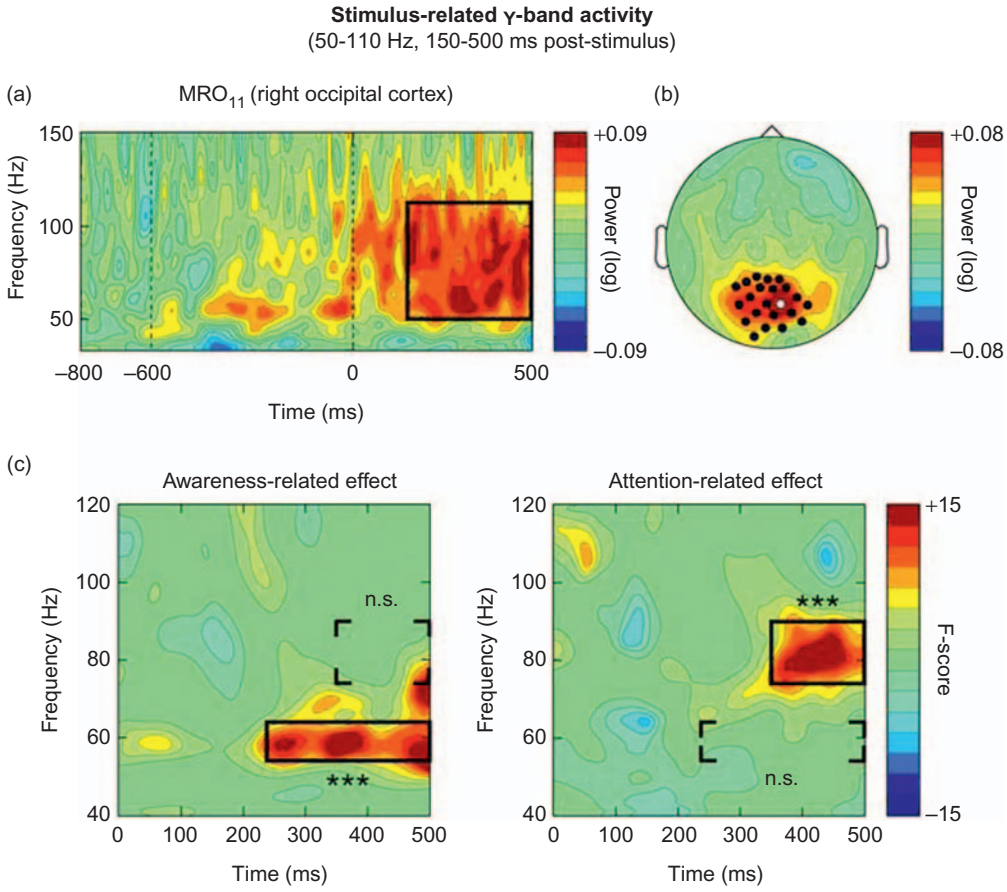


FIGURE 8.37 Separate brain correlates of attention and awareness. Wyart and Tallon-Baudry (2008) were able to dissociate the effect of visual awareness and selective attention. (a) MEG recordings over the right occipital cortex from 100 to 500 ms post-stimulus, as shown in (b), the cartoon of the head. High levels of gamma power were observed over the occipital cortex. The lower graphs (c) show frequency times, displayed with colors indicating the F score of MEG power, a measure of statistical significance. The black, red, and yellow colors show high levels of gamma attributable to the awareness manipulation (left) and the cued attention manipulation (right). Visual awareness increased low gamma power at ~250 to 500 ms (near 60 Hz), while attention involved a higher gamma burst around 80 Hz beginning 350 ms post-stimulus. This is somewhat counter-intuitive, since we might expect the attention effect to precede the awareness effect. One question is whether attentional effects could be detected earlier in frontoparietal regions of the brain. Notice that the significant gamma bursts were compared with the same locus in the time-frequency domain in each graph in post-hoc comparisons. *Source*: Wyart and Tallon-Baudry, 2008.

4.0 REM DREAMS

Not all typical dream experiences occur during REM states, as defined physiologically – by rapid, stereotypical eye movements, waking-type scalp EEG, and sensory-motor blocking. Quite a lot of subjective mental activity occurs during slow-wave sleep, although it does not tend to be the vivid narratives we experience during classical dreams. The sleep architecture of Figure 8.38 gives us a useful outline, but individual sleep stages may be quite different. We will therefore refer to 'REM dreams' as those periods when we have classical subjective, narrative dreams along with REM activity.

Along similar lines, Hobson *et al*. (2000) define *dreaming* as 'mental activity occurring in sleep characterized by vivid sensorimotor imagery that is experienced as waking reality, despite such distinctive cognitive features as impossibility or improbability of time, place, person and actions; emotions, especially fear, elation and anger predominate over sadness, shame and guilt and sometimes reach sufficient strength to cause awakening; memory for even very vivid dreams is evanescent and

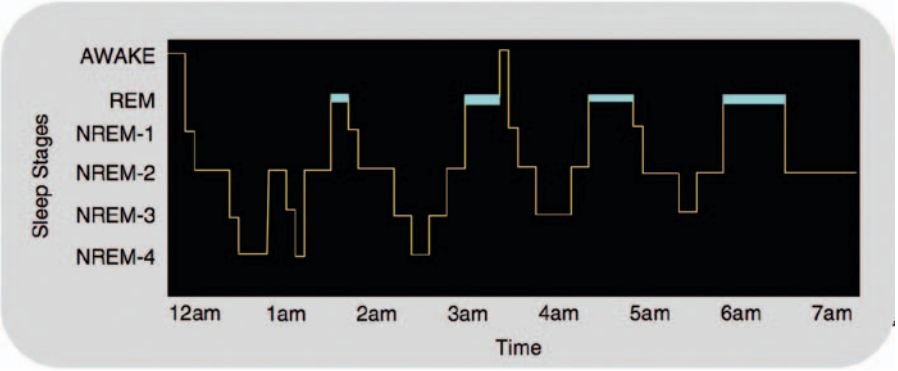


FIGURE 8.38 The architecture of sleep. The thalamocortical core changes dramatically in sleep. In deep sleep, the low, irregular oscillations of waking EEG change to high, slow, and regular activity, called *delta* waves. The four levels of arousability (Stages 1–4) show increasing delta waves, until Stage 4 of Non-REM (NREM-4) is almost all delta. Every 90 minutes or so, sleepers show rapid eye movements (REM) as the eyes swing back and forth. At the same time the EEG shows striking waking-like activity in the EEG: fast, irregular, and low in amplitude. People who are awoken from REM tend to report vivid, narrative dreams, whereas SWS sleepers may report waking-like inner speech. REM periods become longer in the second half of the night. *Source*: Stickgold & Walker, 2007.

tends to fade quickly upon awakening unless special steps are taken to retain it'.

Both sensory input and motor output are blocked during REM dreaming, so that the brain is talking only to itself. The existence of motor inhibition may give rise to some 'paralysis dreams', in which we feel paralyzed, or want to move in the dream, but feel we cannot. This can lead to unpleasant 'locked-in' feelings during dreaming, if we become aware of being unable to move. But muscular inhibition is an entirely normal part of dreaming. For one thing, motor inhibition keeps us from acting out our dreams.

Memory is also impaired during REM dreaming. When dreamers are woken up from REM they may report vivid visual memories, but they tend to fade in seconds unless we make a special effort to rehearse them. It is almost as if we are creating a running movie in our dreams, but we can't recall the storyline from one scene to the next. Even people with good dream recall are likely to remember only a tiny fraction of their nightly 90 to 120 minutes of REM (Figure 8.38).

REM dreaming is triggered by 'PGO waves' – pons-geniculate-occipital activation, along with neuromodulation. Sharp bursts of neuronal spikes come from the pons (P), activate the lateral geniculate nucleus of the thalamus (G), and then trigger visual experiences by way of the occipital cortex (O). Hobson and McCarley, who advanced the early PGO hypothesis in 1976, called this the 'activation-synthesis hypothesis', with the emphasis on the activation burst from the pons and its conscious interpretation or 'synthesis' by the cortex (Hobson *et al*., 2000). An update is given in Hobson *et al*. (2000; Figure 8.39). Pace-Schott and Hobson (2002) write that REM sleep is also triggered by changes in major brain modulators, especially norepinephrine, acetylcholine, serotonin (5-HT), and glutamine.

The PGO theory does not explain the content of dreams. It only suggests that the cortex tries to make a coherent story out of meaningless brainstem signals. What determines dream contents remains a puzzle. Traditional ideas advanced by Sigmund Freud and Karl Jung often are treated skeptically, but few plausible alternatives have emerged. However, there is good agreement on the high emotional content of dreams.

Revonsuo and colleagues have proposed a Threat Simulation theory of dreams, an evolutionary hypothesis based on the fact that the REM state is widely observed in mammals and birds, and therefore may have an important evolutionary function. Revonsuo (2000) suggests that dreams allow us to mentally rehearse threatening situations. Traumatized individuals may reexperience events related to the trauma (in some cases even during the waking state). Consistent with their theory, Valli and Revonsuo found that traumatized children from a war zone had significantly more threatening dreams than controls. Other major life events, such as loss of a loved one, or even normal stressful events, might also be reflected in dream contents. Spontaneous waking thoughts tend to rehearse current concerns, and dream contents may repeat the same themes. It remains to be shown, however, whether dreaming also supports coping strategies, as we might expect if dreaming had an evolutionary threat-related function.

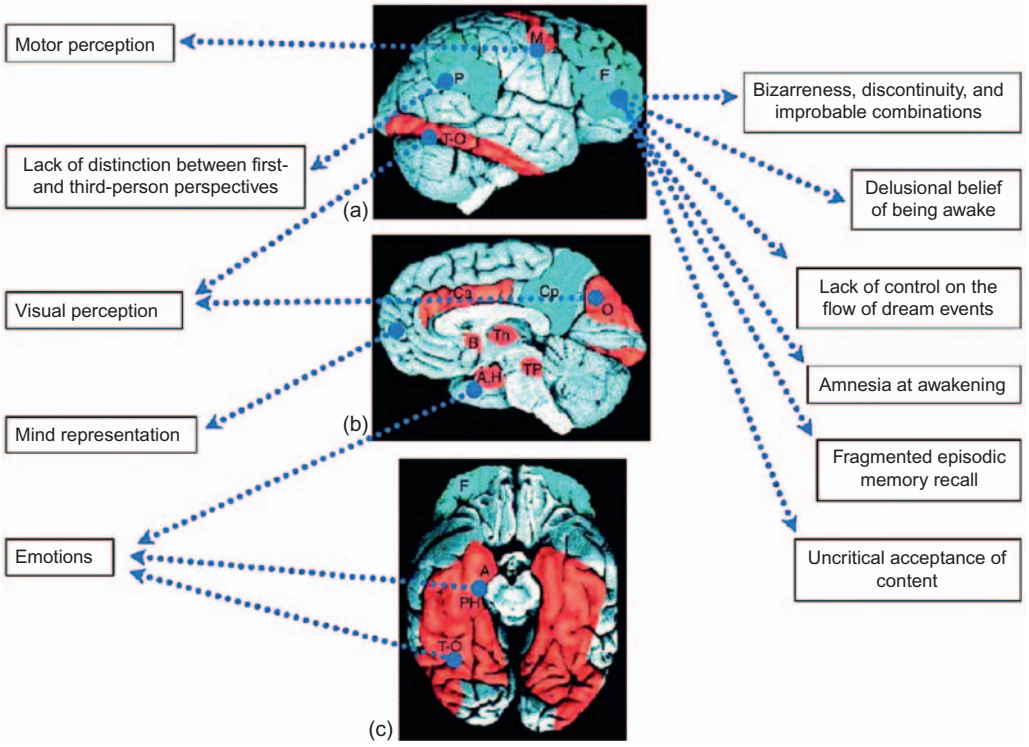


FIGURE 8.39 Functional brain imaging of REM dreams. fMRI activity during dreaming. Red areas represent increased blood-oxygen-related activity, for example in emotion areas. Blue areas correspond to below-baseline activity during dreaming, as in the frontal lobes. Higher activity in occipital regions may reflect vivid visual dream imagery. Low frontal lobe metabolism may also explain the delusional beliefs, bizarreness, and sudden discontinuities of dreams, such as rapid changes in scenes, dream characters, and narrative coherence. Low frontal lobe functioning is consistent with amnesia for dreams upon awakening, and low levels of voluntary control. *Source*: Dang-Vu *et al*. in Squire, 2009.

TABLE 8.3 Major features of REM dreams

Hallucinations – especially visual and motoric, but occasionally in any and all sensory modalities
Bizarreness – Incongruity (imagery is strange, unusual, or impossible; Discontinuity (imagery and plot can change, appear or disappear rapidly); Uncertainty (persons, places, and events often bizarrely uncertain by waking standards)
Delusion – we are consistently duped into believing that we are awake (unless we cultivate lucidity)
Self-reflection absent or greatly reduced – relative to waking
Lack of orientational stability lack – persons, times, and places are fused, plastic, incongruous, and discontinuous
Narrative story lines – explain and integrate all the dream elements in a confabulatory manner
Emotions increased – intensified and predominated by fear-anxiety
Instinctual programs – (especially fight-flight) often incorporated
Volitional control – greatly attenuated
Memory deficits – across dream-wake, wake-dream, and dream-dream transitions

Source: Hobson, J.A in squire ***et al.***, 2008.

4.1 Dreaming as a conscious state

Dreams tend to be reported *as* conscious when people are woken up during REM and asked to describe what they were experiencing in the seconds before. The EEG of REM dreaming is strikingly similar to wakefulness, containing alpha, beta, gamma, and theta frequencies in a complex mix. It therefore seems that we actually have *two* daily conscious states: Waking and REM dreaming. The electrical activity of waking and dreaming reflects a similar operating style by the thalamocortical system. However, it is important to keep in mind that there are important differences during REM as well, such as sensory and motor blocking, a high level of emotional activity, and a low level of executive (frontal lobe) control.

The surreal and nonrational nature of dreams may reflect this lower level of executive control. Dreaming is a 'hypofrontal' state, like drowsiness, alcohol inebriation, delirium, and other states of lowered self-reflection and self-control (Dietrich, 2002). In addition, the limbic regions of the brain, which are involved with emotions, show higher fMRI activity than the waking state (Figure 8.39 and Table 8.3).

Some people learn to experience their dreams *knowing* they are dreaming, and even to exercise some voluntary control during dreaming. LaBerge *et al*. (1981)

made a case for such 'lucid dreaming' in the sleep laboratory by showing that some dreamers could learn to voluntarily move their eyes back and forth three times in a row, on cue, when given an auditory signal. Some lucid dreamers could also count to ten in the dream, and then show the experimenters that they had done so by repeating the triple eye movement to signal the end of the ten-second period. Lucid dreamers in this experiment had to recall and carry out their task instructions, learned during the waking period before going to sleep. Thus lucid dreaming required executive functions and semantic memory retrieval, as well as linguistic and auditory processing. Lucid dreamers may therefore be able to control some of the cognitive functions that usually are impaired in the REM state.

4.2 Memory consolidation in REM

Debate continues over the role of REM dreams in memory consolidation, with findings reported pro and con. However, *emotional* memories seem to be consolidated by REM dreams during afternoon naps – which are easier to study than overnight dreams – when compared to emotionally neutral materials (Nishida *et al*., 2009). Both emotions and REM involve ancient mammalian brain systems. There is a three-way overlap between brain regions for episodic learning (hippocampal complex and neocortex), emotion (hippocampus, amygdala, and neocortex), and dreaming (limbic activation, thalamus, and neocortex). Emotionally evocative experiences are the ones that humans need to remember if we are to improve our chances for reproductive success. We need to avoid those dangerous wild animals the next time we see them, or remember which of our clan members gave us food and shelter. Emotions have to do with our personal and interpersonal welfare: fear, attraction, safety, love, hunger and satiety, anger, envy, pride; those are the experiences we must remember.

The stress hormone cortisol is involved in emotional experiences as well as memory consolidation. Cortisol increases during the night, as does the likelihood of REM dreaming (Payne and Lynn Nadel, 2004). More than 80% of SWS is concentrated in the first half of the night, whereas the amount of REM dreaming doubles in the second half.

A number of studies have reported increased theta rhythm coupling between the hippocampus and frontal lobe during REM sleep. Since memory consolidation is believed to require that kind of theta-band coordination, those findings support a role for REM in the consolidation of memories (Hobson & Pace-Schott, 2002). However, the best emerging evidence for memory consolidation comes from advancing knowledge about gene expression required for protein manufacture needed to grow new synapses and other cellular structures needed for enduring memories. So far this is largely a literature on other mammals. The number of genes that are believed to play a role continues to increase as we learn more (Figure 8.40). Thus we are in the midst of a major wave of new evidence, and we can cite only a few examples (see Chapter 16). Nevertheless, the evidence for consolidation through gene expression is likely to be more definitive than anything else we have so far.

Figure 8.40 shows one kind of consolidation-related gene expression in the rat as a function of brain state. The gene is Zif-268, and its expression is fluorescence-tagged, so that immediately after learning, the rats are sacrificed and we can see color-coded fluorescent activity in different parts of the brain. The figure shows six left coronal sections of the rat brain rapidly obtained during waking, slow-wave sleep, and REM. Notice that both the enriched environment and the control condition lead to moderate to high levels of Zif-268 expression in the waking state (WK) (yellow and red colors). Most expression occurs during waking states, with REM playing a secondary role, and slow-wave sleep coming in last. Keep in mind, however, that these are still early days for the study of gene expression for memory consolidation. Hundreds of different genes are believed to be involved in learning, and this study is primarily an example of what is likely to emerge in the near future (Knapska & Kaczmarek, 2004).

5.0 DEEP SLEEP: UPS AND DOWNS

Slow-wave sleep (SWS) is a cognitively active state, even though it is the least conscious time of the daily cycle. SWS may allow the replay and consolidation of memories acquired during waking.

One recent discovery is the role of 'slow oscillations', defined as very widespread cortical waves as slow as 0.01 Hz, and peaking around 0.75 Hz.There is debate whether Slow Oscillations (SO) are the lower end of the traditional delta range, which is easily seen in the raw EEG. Delta is considered to be 1 to 3 Hz, but all EEG frequency bands are somewhat tentative, because we continue to learn more about them.

Slow Oscillations are seen as a series of gradual peaks and valleys in brain activity, known as Up and Down States. Each of those half-waves may last from 0.5 sec to tens of seconds. The Up half-wave of the SO

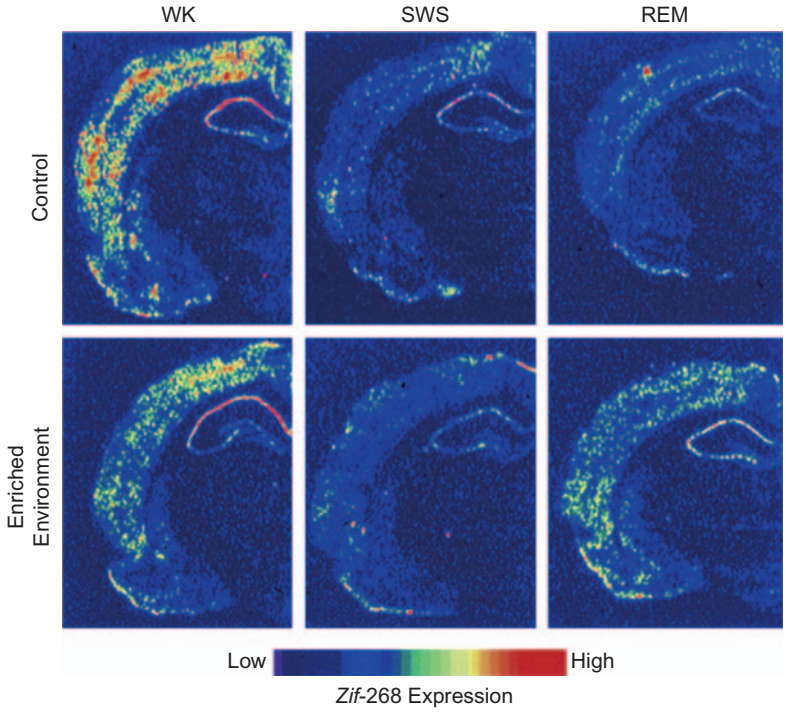


FIGURE 8.40 Gene-controlled protein manufacture for memory consolidation. The best evidence for memory consolidation comes from animal studies of gene expression needed to manufacture the proteins needed for memory consolidation. We are just beginning to see studies of perhaps hundreds of genes that are believed to be involved in memory consolidation. Above, slices of the left halves of rat cortex that were rapidly frozen immediately in each state, and subjected to fluorescent chemical labeling for the gene zif268. The primary comparison is between the Enriched Environment, believed to support increased learning, and a Control condition. In the lower right hand slice, higher REM gene expression is obtained in the Enriched Environment group compared to the Controls. Waking involves more Zif-268 expression than REM, and REM more than slow-wave sleep. *Source*: Knapska & Kaczmarek, 2004.

is believed to allow for a waking-like moment of brain activity (Destexhe *et al.*, 2007). During the Up State neurons can freely signal to each other, so that theta and gamma interactions can take place. In contrast, the Down State is thought to lower thalamocortical activity to its baseline level. The Up State of SWS therefore could be considered to be an active waking-like event, whereas the Down State seems to block most neuronal interactions. What is really distinctive about SWS therefore might be the regular Down States, occurring every few seconds, and interrupting the waking-like Up States long enough to prevent integrative processing. If you imagine having to stop talking every other second in a normal conversation, you can see how much that would interfere with normal thinking and speaking.

Slow Oscillations are believed to *group* faster waveforms – theta, alpha, beta, and gamma. By analogy, the slow rise and fall of the ocean tides group six-foot beach waves that ride on top of the tides. Six-foot waves in turn group smaller choppy waves. In the actual sea, that kind of grouping by slower waves occurs by literally lifting up smaller waves, which flow on top of the slow tides and larger breakers. Such a hierarchy of waves makes for an attractive simplification, and as we will see, there is evidence to support it.

A physiological mechanism for grouping of faster rhythms by slower ones is easy to imagine: The Up State of Slow Oscillations involves massive neuronal firing, making downstream neurons more likely to depolarize and fire their own axonal spikes. Neurons involved with faster waveforms therefore receive more dendritic inputs, and increase their graded potentials to come closer to the threshold of a depolarizing spike. Slow Up States can therefore be imagined as adding a voltage increment to large numbers of neurons, making them more likely to fire and interact. Down States would have the opposite effect. Such a very broad effect of slow waves might occur through volume conduction, by means of widespread neuromodulation, or by neuron-to-neuron synaptic signaling (Chapter 3).

5.1 Some mental activity occurs even in slow-wave sleep

People awoken from slow-wave sleep report ongoing mental contents about half the time. Steriade (2006) writes that 'in contrast with the assumption that dreams occur entirely in REM sleep, a series of studies, starting with the 1960s, has demonstrated the presence of dream mentation during slow-wave sleep. Slow-wave sleep thinking is rational and repetitive, whereas during REM sleep the internal perceptions are vivid, thought becomes illogical, and the intensity of emotions is higher than during slow-wave sleep'. During REM sleep, dream recall may occur about 95%

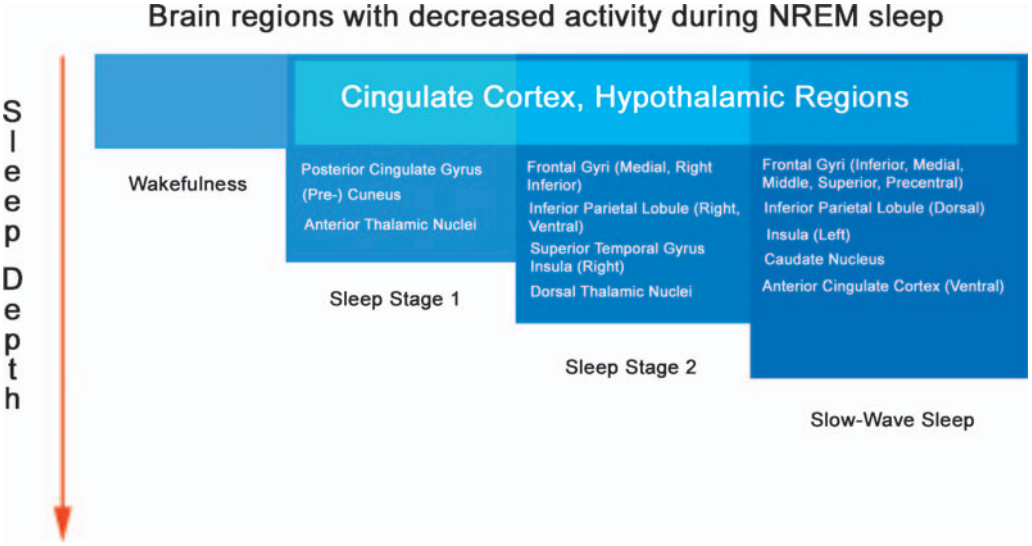


FIGURE 8.41 Regional metabolism declines with depth of sleep. As the arousal threshold goes deeper, and sleepers are more difficult to arouse, more slow waves are visible in the EEG, and metabolic activity goes down in more parts of the brain. But deep sleep still has biological functions, as in the 'replaying' of hippocampal firing patterns of episodes acquired in the preceding day. *Source*: Adapted from Hobson, J.A in Squire, L. (ed.), 2009.

of the time; outside of REM, reports of mental activity fall to about 50%. Steriade concludes that 'the brain is never 'empty', and mental activity is present during all stages of sleep' (2006, p. 1098).

Why do we have the belief that deep sleep is completely unconscious? One possibility is that arousability goes down as slow waves begin to dominate electrical brain activity (Figure 8.18). Lower arousability means that it takes longer to wake up, and a longer time to full arousal means that our memory for sleep mentation may be worse. Memory can fade in seconds. Some individuals 'wake up very slowly', suggesting that their frontal lobe function does not reach full waking levels for some time after they become perceptually conscious. In the study of the circadian sleep cycles some people are called 'larks' (they feel alert in the morning) and 'owls', who feel groggy in the morning and have their peak of alertness later in the day.

5.2 The arousal threshold changes during sleep

The depth of sleep is measured by the arousal threshold – whether a human or animal will become alert to a stimulus and orient to it. The arousal threshold goes up as slow waves increase in the EEG (Figure 8.41). Most slow-wave sleep tends to occur earlier in the night, and most REM dreams happen in the second half.

Figure 8.41 shows lower metabolic activity spreading in the brain as sleep becomes deeper (as defined by ease of arousal). Brain metabolism declines in a specific order, beginning with midline cingulate structures that have been associated with 'self-orientation' and their corresponding thalamic nuclei. In slow-wave sleep (Stages 3 and 4) metabolism is decreased in the active 'cognitive' parts of the brain. However, sensory cortex remains relatively active, although the flow of sensory stimuli is blocked at thalamic relay nuclei.

5.3 Memory replay and consolidation

It is difficult to study the effects of SWS separately from REM, because they constantly go together. However, SWS is more common in the first half of the night, whereas REM predominates in the second half. Researchers therefore have studied memory consolidation after 'SWS-rich' and 'REM-rich' periods of sleep. In general, SWS-rich periods appear to strengthen explicit memories, and REM-rich periods strengthen procedural tasks and perhaps implicit memories. Increased SWS has been observed after intensive episodic learning, and increased REM after procedural training.

Other studies focus on the role of the hippocampal region in the acquisition of episodic (conscious) memories (Figures 8.42 and 8.43). Episodic memories are

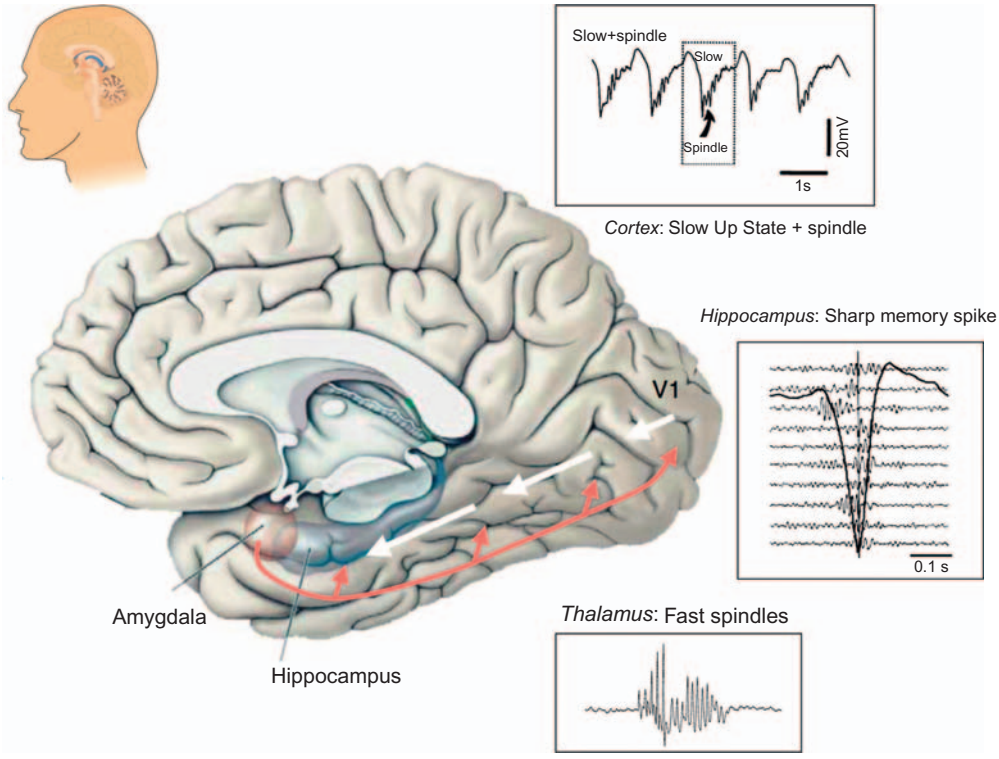


FIGURE 8.42 Slow-wave sleep enables memory consolidation during 'Up States'. How slow-wave sleep is believed to enable memory consolidation. Three brain regions work together: Early episodic learning during the waking state encodes labile (unstable) hippocampal and neocortical memory traces. During slow-wave sleep thalamic spindles ignite Up States, which triggers hippocampal sharp spikes, which finally are believed to activate synchronized memory traces in the hippocampus. Thus thalamic spindle activity helps to trigger the next Up State, as shown by cortical iEEG. These regions act in concert to reactivate recent memory traces. During the following Down State of SWS the activated neurons are believed to express proteins that lead to synaptic plasticity for more enduring memory coding. Adapted from Steriade, 2000.

thought to be transferred from the hippocampus to the neocortex in order for memories to become enduring. In rodents the hippocampal region has been studied for decades, using direct brain recording in maze learning. The hippocampus plays a major role in place learning and navigation, and it has been possible to pinpoint hippocampal 'place cells' that fire when the animal passes a particular point in the maze. As the rat runs the learned maze, place cells fire in sequence. Afterward the same pattern of cell firing is observed during slow-wave sleep, activating other parts of the brain, like the thalamus, neocortex, and basal ganglia (Figures 8.42 and 8.43). In sum, in rats we can actually record neurons when the animals are exploring locations in sequence, and observe that the brain replays a learned spatial sequence during SWS. The theta rhythm appears to be a major organizing and transmission rhythm for the hippocampal-neocortical dialogue that leads to memory consolidation (Jensen, 2005; Buzsaki, 2002).

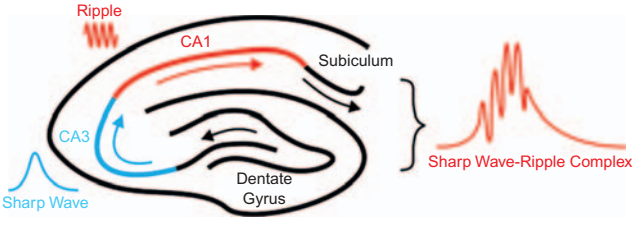


FIGURE 8.43 Hippocampal Sharp and Ripple Waves. A cartoon of the hippocampus shows its basic arrays of neurons, which generate Sharp Waves and Ripple Complexes in activating retrieval and neocortical consolidation during slow-wave sleep. *Source*: Beenhakker and Huguenard, 2009.

Humans have also been studied in learning to navigate a virtual town, using a video game. After learning the town, similar hippocampal activity was again found to reactivate during SWS. The amount of reactivation correlated with recall on the following day. Thus the human and animal evidence points to the

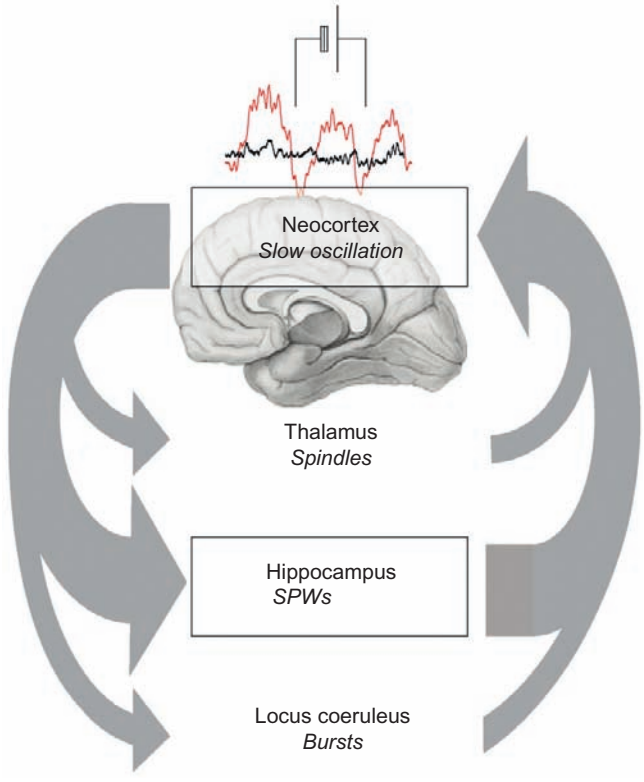


FIGURE 8.44 Artificial induction of slow waves. Individual slow oscillations can be enhanced by electrical field induction over the scalp. Notice that induced slow oscillations also evoke thalamic spindles and hippocampal sharp waves, which work together to enable hippocampal memory retrieval and consolidation. *Source*: Marshall and Born, 2007.

same basic conclusions (Colgin *et al*., 2009; Vertes & Kocsis, 1997).

The hippocampus has many of the functions of the brain as a whole, because it was once the core brain of ancestral mammals. The larger hippocampal system is involved in spatial navigation and in marking emotionally significant experiences, as well as in goal-guided control of behavior, episodic and declarative memory encoding and retrieval, and in SWS memory consolidation. Different neuronal arrays (CA1 and CA3) generate Sharp Waves and Ripples, which are multiplexed together (as in the Sharp Wave-Ripple Complex on the right). As the previous figure shows, these rhythms enable retrieval of active memories learned during the waking state, and their replay and consolidation in the neocortex.

Some of the best evidence for SWS memory consolidation comes from the use of transcranial brain stimulation to entrain slow oscillations in the cortex. Once these oscillations are under experimental control, direct causal hypotheses can be tested. Figure 8.44 shows how it is done. A subject learns a task and goes to sleep several hours later in a sleep laboratory, wearing an EEG electrode cap. As natural SWS is observed in the EEG, an electromagnetic coil located over the head is pulsed slowly (<1 Hz), to enhance the slow oscillations. Simultaneous recording shows a slow wave in the cortex, along with typical thalamic spindle waves and hippocampal sharp waves (SPWs).

In a sham control condition the identical procedure is performed without electromagnetic stimulation, to control for placebo effects. Transcranial slow-wave stimulation during SWS was found to improve episodic but not procedural memories. It seems that artificial slow-wave induction improves the natural SWS conditions for memory consolidation.

Notice that we now know several brain rhythms that play essential roles in memory consolidation during SWS.

1. Slow oscillations cycle at < 1 Hz, but may overlap with the delta range of 1–3 Hz. During Up States, the peaks of slow oscillations, fast neuronal firing, and interactions are possible, much like the waking state. But during the Down States of SWS, the cortex and thalamus go silent.
2. The slow Up State also groups theta activity, cycling at 4–7 Hz. Theta is known to be involved with hippocampal organization of learned information, and with transmission of that information to the neocortex.
3. Theta waves 'group' faster gamma activity, both within the hippocampal complex, and in encoding sensory information in the hippocampus (from visual cortex, for example). Theta also carries hippocampal messages to the frontal lobes and other parts of the neocortex during memory consolidation.
4. Gamma activity (30 Hz and above) is embedded in theta activity, and also serves to synchronize hippocampal and neocortical neurons. A number of scientists believe that it is gamma activity that actually carries the most detailed information, grouped by slower oscillations. Gamma is now known to have a very wide range (by some estimates, 25–120 Hz, with some activity even at 600Hz and 1200 Hz).

In all these cases, slower waves are believed to increase the probability of the next faster wave. The Up State of the Slow Wave enhances theta, theta enhances gamma, and gamma recruits synchronous firing of individual neurons and groups of neurons in the hippocampus and neocortex.

6.0 PUTTING IT ALL TOGETHER

Consciousness has intrigued humans since the beginning of history. With improved brain and cognitive techniques we can see considerable progress in recent years. We will review this chapter by looking at some popular proposals about consciousness and attention.

6.1 Does consciousness reflect a global workspace function in the brain?

The idea that consciousness has an integrative function has a long history. Global Workspace Theory (GWT) is a cognitive architecture with an explicit role for consciousness in humans. It suggests that conscious contents involve a fleeting integrative memory capacity in the brain, in which only one consistent content can be dominant at any given moment (Baars, 1988, 2002). Potentially conscious events compete for access to the limited-capacity workspace. In the attentional model described earlier, this competition is accomplished by a Winner-Take-All network (Itti & Koch, 2000).

GWT proposes that momentarily dominant information is widely distributed in the brain. That makes sense in a nervous system viewed as a massive distributed set of special-purpose networks. In such a system, coordination, control, and novel problem solving could take place by way of a central information exchange, allowing some regions – such as sensory cortex – to distribute information to the whole. This strategy is particularly useful for dealing with novel problems that do not have a known solution, and that may be solved by the collaborative and/or competitive activation among numerous specialized networks, each of which may contribute toward a solution. Such an approach works well in large-scale computer architectures, which show typical limited capacity behavior when information flows by way of a global workspace (Baars, 2002).

A body of evidence now indicates that consciousness is the primary agent of such a global access function in humans and other mammals (Baars, 2002; Dehaene, 2001). Dehaene and colleagues used visual backward masking to compare conscious and unconscious words, using a pattern mask presented immediately afterward. Masked words are unconscious, but they are not physically blocked from entering the eyes. Brain imaging analysis showed that both conscious and unconscious words activated the cortical vision and word recognition areas, which are known to analyze stimulus location, shape, color, and word identity. However, conscious words triggered 12 times more activity in these regions than identical unconscious ones. In addition, conscious words evoked a great deal of additional activity in the parietal and frontal cortex. It seems as if the stimulus-related activity in the conscious case may be widely distributed from visual regions to other areas in the brain.

Conscious involvement is particularly useful when novel information needs to be combined and integrated, and when it needs to recruit additional brain resources. That is presumably why episodic memory (memory for conscious events) is so central in brain anatomy, with the hippocampal complex and neocortex engaged in a constant dialogue for storing and retrieving episodic/declarative memories. Even implicit learning is mobilized by conscious cues, as described in this chapter.

GWT generates testable hypotheses regarding conscious and unconscious aspects of perception, learning, working memory, voluntary control, and self systems in the brain. It has close similarities to other biological theories such as Neural Darwinism and dynamical theories of brain functioning (Edelman & Tononi, 2000). Dehaene and others have developed experimentally testable models for aspects of the theory (Dehaene, 2001). A number of experiments have led to generally positive results.

Dehaene and colleagues (2001) proposed a neuronal implementation of a global workspace architecture, called neuronal global workspace (Figure 8.45). In this model, sensory stimuli mobilize excitatory neurons with long-range cortico-cortical axons, leading to the genesis of a global activity pattern among workspace neurons. Any such global pattern can inhibit alternative activity patterns among workspace neurons, thus preventing the conscious processing of alternative stimuli. The global neuronal workspace model predicts that conscious presence is a nonlinear function of stimulus salience (i.e., a gradual increase in stimulus visibility should be accompanied by a sudden transition of the neuronal workspace into a corresponding activity pattern). Such 'ignition' of the workspace is consistent with the notion that consciousness is an all-or-nothing, as opposed to a graded, process. The neuronal global workspace has been used to model a number of experimental phenomena in consciousness. In one study, spontaneous workspace activity blocked external sensory processing, in a manner analogous to inattentional blindness, in which normal subjects engaged in effortful mental activity fail to notice salient but irrelevant stimuli.

A similar phenomenon is the attentional blink, in which subjects are unable to report a stimulus S2 presented within a short time interval (100–500 ms) following the presentation of a first stimulus S1. In a neuronal

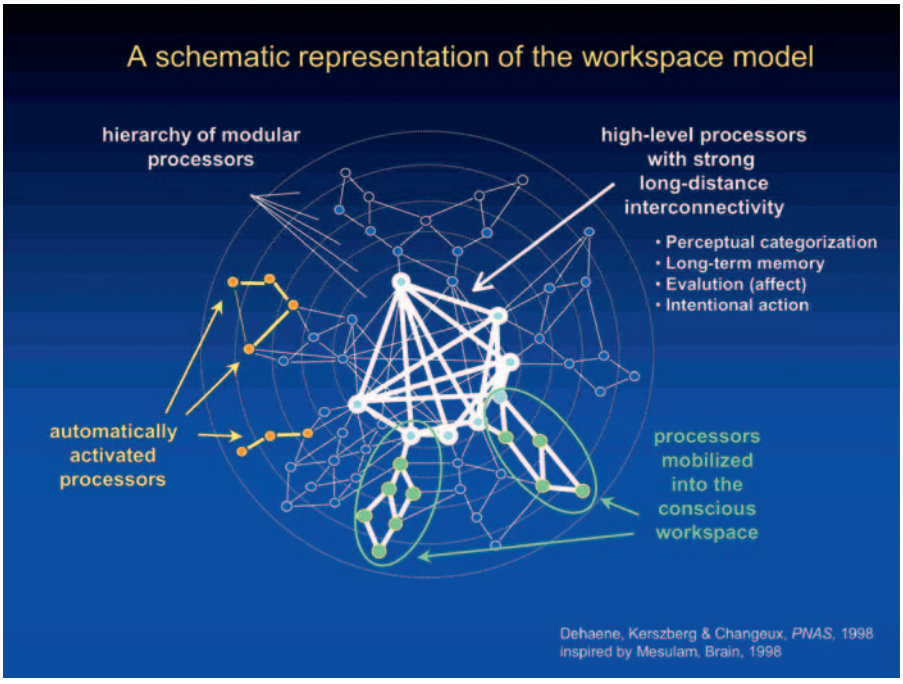


FIGURE 8.45 A neural global workspace to support conscious experiences. Dehaene *et al*. (2001) proposed a neuronal global workspace model, attributed to long-distance interconnectivity of the prefrontal cortex. Other specialized regions of the cortex are selectively mobilized into the conscious workspace. Most brain networks are activated automatically (unconsciously). The model accounts for major brain functions like perceptual categorization and long-term memory, as well as experimental paradigms like the attentional blink and visual backward masking. *Source*: Dehaene, with permission.

global workspace model of this paradigm, the presentation of S1 evoked both bottom-up and top-down signal flow, leading to the sort of sustained activity that might underlie conscious reportability in human subjects. However, the presentation of S2 immediately after S1 evoked only bottom-up activity because of the global activity constraints imposed by S1. This decay of sustained activity relating to S2 may reflect the lack of conscious access in the attentional blink effect.

A number of scientists have now published evidence consistent with this framework. The broadcasting hypothesis is probably the most distinctive hypothesis. That is, conscious contents are proposed to recruit multiple brain resources, a process that involves global distribution of information (both in the brain, and in the original artificial intelligence models that utilized a global workspace). In a 'society model' of the brain, comparable to the World Wide Web, the details of information processing are left to a large number of local networks. The role of the global workspace, like a chat room on the Web, is to allow the interaction of multiple streams of goal-directed processes, and to broadcast dominant messages from among those potentially competing streams. As in an Internet chat room, some voices may be more dominant than others, and the most consistently dominant ones have the widest outreach. At the same time multiple processing streams are running outside of the chat room, or in this case, outside of the global workspace.

A number of findings show that conscious cognition is distinctively associated with the wide spread of cortical activity, notably toward frontoparietal and medial temporal regions (see Chapter 1). It is essentially to use unconscious comparison conditions in experimental tests of any theory of conscious functions. Current evidence indicates that unconscious comparison conditions tend to activate only local regions, such as local visual processes. These findings are consistent with GWT, which is now favored by a number of scientists and philosophers (Baars, 2002). Baars and Franklin (2005) also have proposed that conscious moments are essential to recruit Working Memory functions like mental rehearsal, encoding, retrieval, and voluntary report.

An alternative hypothesis is that, because any conscious event is presumed to be reportable, the prefrontal-parietal component may be related to readiness to report rather than conscious experience as such. This is a difficult alternative to test conclusively. As we gain a more detailed understanding of the specific functional regions of the cortex, it may become possible to do so.

Many sources of evidence suggest that conscious events show wider cortical activity than matched comparison cases. A major theoretical question, therefore, concerns the contribution of frontoparietal activity in conscious perception.

Unconscious states show the other side of the global broadcasting hypothesis: they show frontoparietal hypometabolism in deep sleep, coma, vegetative

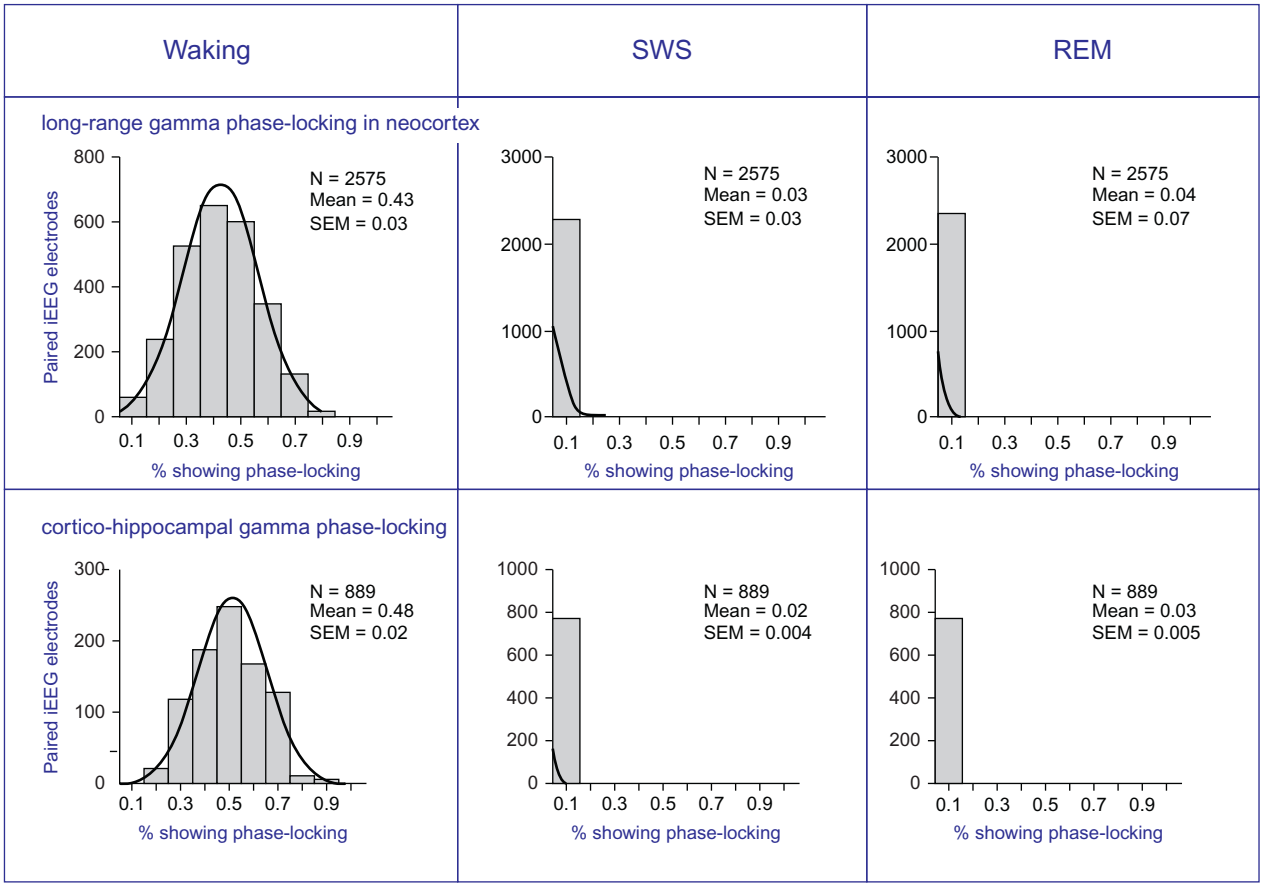


FIGURE 8.46 Long-distance gamma phase-locking in Waking, SWS, and REM. The upper row shows iEEG neocortex and the lower row shows hippocampal-cortical iEEG. Waking shows consistent gamma phase-locking averaging near 50%. Gamma is defined as 35–58 Hz. The horizontal axis refers to percent of all possible combinations of electrodes showing phase locking. (Similar values were obtained for state-dependent local gamma coherence.) *Source*: Cantero *et al.*, 2005.

states, epileptic loss of consciousness, and general anesthesia (see Baars *et al*., 2003; Blumenfeld, 2008). We are seeing broadly consistent lines of evidence.

Figure 8.46 from Cantero *et al*. (2005) shows that long-distance gamma phase-locking, which reflects fast information transmission, is distinctively associated with the waking state, but not SWS or REM. This study was performed in presurgical epilepsy patients with implanted intracranial electrode grids, and therefore represents the highest signal-to-noise ratio obtainable at the present time. Notice that long-distance gamma phase locking occurs both within the neocortex itself, and also between the hippocampus and cortex.

As mentioned before, gamma activity is believed to be carried on slower wave forms. The 100-ms domain is especially important, since it represents the minimum conscious integration time in perception, for example. That is, two discrete sensory events in any modality can be integrated into a single conscious event only if they occur within 100 ms of each other (approximately). The 100-ms integration time does grow much larger in speech or music perception, or dance performance, where momentary events are interpreted in a much longer contextual framework. But for separate conscious events, like fast clicks, brief tones, visual flashes, sensory taps, and so on, the approximately 100-ms integration time seems to hold up well. Other sources have also suggested a 100 ms or 10 Hz series of conscious microstates, due to evidence from EEG and other sources (Freeman, 2006; Lehmann, 2010).

It is therefore interesting that Doesburg and colleagues (2008), using MEG recording of visual stimuli, found approximately 100 ms momentary gamma phase-locking across large regions of cortex in response to lateralized visual signals. This is precisely what we might expect for a momentary conscious 'broadcast' of momentary visual inputs (Figure 8.47). Notice that there is no synchrony in the first 200 ms after the stimulus,

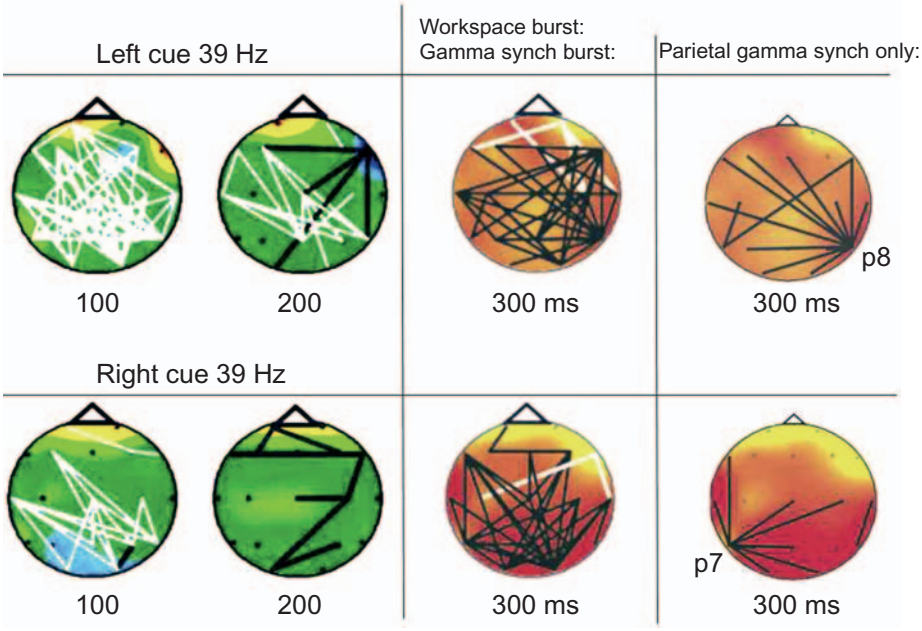


FIGURE 8.47 A moment of conscious activation? Doesburg *et al*. (2007) used MEG to observe long-range gamma synchrony bursts 300 ms after the onset of a visual cue lateralized to the right or left side. Significant synchrony at 39 Hz between sensor locations is indicated by black lines, and desynchrony is shown by white lines. A visual stimulus was presented to the right or left of the fixation point. At 100 and 200 ms, desynchrony predominated, with the emergence of some long-distance synchronized oscillations (black lines). At 300–400 ms synchrony dominated at numerous sensor sites. In the right-most column only parietal sensors are shown. Black lines indicate high synchrony contralateral to the visual stimuli, as would be expected from the cross-wired anatomy of the cortex. From parietal sources (P7 on the left, and P8 on the right) activity can be seen to spread to both ipsilateral and contralateral regions of cortex. This evidence is consistent with the hypothesis of global brain-wide broadcasting during a conscious moment of about 100–300 ms in duration. Since theta and alpha cycle at about that rate, the claim is that alpha or theta may carry gamma phase-locked activity in multiples of 100 ms bursts. *Source*: Doesburg *et al*., 2007.

but that from 300 to 400 ms a brainwide burst of gramma phase locking occurs. (Phase-locking involves synchrony with a possible brief lag time, and is used here as a more inclusive term.) The right-most column of Figure 8.47 shows only the parietal sensors on the other side of the cortex from the visual signal (i.e., contralateral) making momentary gamma phase-locking bursts for about 100 ms, virtually a visual picture of what is meant by 'global broadcasting' in the brain. These data are consistent with other studies showing a special role for theta or alpha signals, since these slower waveforms oscillate near 10 Hz, and therefore might provide the appropriate carrier waves for gamma phase-locked fast oscillations.

Notice that we now have a number of separate sources of brain evidence showing coherent gamma bursts in association with conscious perceptual moments, paced by rhythms near theta or alpha. In order to test whether this applies to conscious, but not necessarily unconscious, events, a number of laboratories have used binocular rivalry, visual backward masking, the attentional blink, and other methods. Doesburg *et al*. (2009) used binocular rivalry to 'Reveal Large-Scale Oscillatory Network Dynamics Mediating Visual Perception'. They write,

> We propose that discrete moments of perceptual experience are implemented by transient gamma-band synchronization of relevant cortical regions, and that disintegration and reintegration of these assemblies is time-locked to ongoing theta oscillations.

Using somewhat different experimental methods and analytical tools, Gaillard *et al*. (2009) also concluded that

> … nonconscious processing of masked words was observed in multiple cortical areas … but without

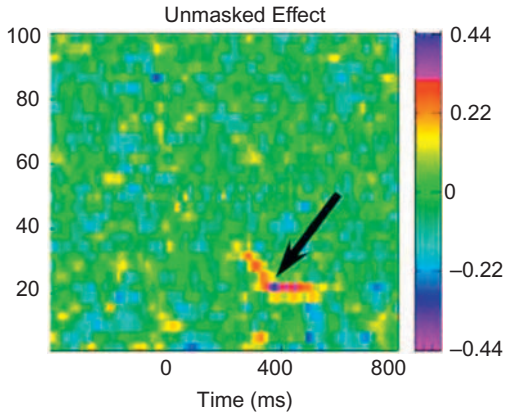


FIGURE 8.48 Long-distance gamma synchrony in conscious, but not unconscious vision. The difference between conscious and unconscious visual input is shown in this experiment by a brief but statistically significant long-distance gamma synchronous burst slightly above 20 Hz. (Arrow) Four convergent measures signaled a difference between the two conditions, including Granger causality, which allows the statistical extraction of causally related activities in complex and parallel time series, such as we constantly see in the brain. *Source*: Gaillard *et al.*, 2009.

> coherent long-distance neural activity, suggesting a quickly dissipating feedforward wave. In contrast, conscious processing of unmasked (conscious) words was characterized by the convergence of four distinct neurophysiological markers: sustained voltage changes, particularly in prefrontal cortex, large increases in spectral power in the gamma band, increases in long-distance phase synchrony in the beta range, and increases in long-range Granger causality. We argue that all of those measures provide distinct windows into the same distributed state of conscious processing.

Figure 8.48 shows the critical difference between conscious and unconscious stimulus conditions in the experiments by Gaillard *et al*. It appears as a single, high-amplitude synchrony burst just above 20 Hz, and 400 to 550 ms after stimulus onset. This graph represents a subtraction between the conscious and the unconscious conditions (called the 'Unmasked Effect' because the control was a visually backward-masked and therefore unconscious stimulus).

The convergence between different sources of evidence is by now striking. When careful brain monitoring is performed, especially using sensitive measures like intracranial recording, brief gamma phase-locking between distant parts of the cortex is observed in conscious, but not closely matched unconscious conditions. This gamma phase-locking appears to be carried by somewhat slower waveforms in the theta-alpha frequency domain. We have seen similar effects in a variety of studies throughout this chapter. At a gross level the same kinds of activities can be recorded in the surface EEG and MEG, in changes of conscious state during sleep and other unconscious conditions, and in a number of cognitive tasks. Such a convergence between different sources gives us greater confidence that the emerging understanding of these hotly debated questions is indeed real.

6.2 Reentrant signaling and complexity in conscious brain events

Because the thalamocortical complex has interactive connectivity compared to other structures like the cerebellum, this part of the brain has been the focus of this chapter. Gerald Edelman and colleagues have provided detailed theoretical studies of the thalamocortical system, in the framework of Neural Darwinism (ND). ND suggests that brain development and dynamics are selectionist in nature, not instructionist, in contrast to computers, which carry out explicit symbolic instructions.

Selectionist processes have four basic features, analogous to living species:

1. A set of elements (neurons, synapses, or dynamic cell assemblies) is characterized by diversity, such as populations of neuronal groups in the brain.
2. These elements can reproduce or amplify.
3. A process of selection operates on the products of diversity; for example, differential reproductive success serves to select some offspring and not others.
4. 'Degeneracy' or functional redundancy, the ability of different combinations of elements to perform the same function, is inherent in such systems. Functional redundancy is a standard feature of human engineered systems, just as it is a routine feature of biological organisms.

In the brain, selectionism applies both to neural development and to moment-to-moment functioning. Selection in the brain is directed by value, which reflects the salience of an event and can be positive or negative. Value is similar to selective pressure in evolution. In the brain, it involves pleasure, pain, and emotional salience. Finally, according to ND, spatiotemporal coordination in the brain is enabled by reentrant signaling, the recursive exchange of signals among neural areas across massively parallel reciprocal connections.

According to Gerald Edelman, the neural systems underlying consciousness arose in evolution as a result

of their ability to integrate a large number of sensory inputs and motor outputs in parallel. This allowed for the discrimination of sensorimotor signals in a high-dimensional space, allowing for the selection of adaptive behavior. Primary (sensory) consciousness is associated with an interaction between perceptual categorization and memory, where primary consciousness refers to the presence of a multimodal scene of perceptual and motor events. It provides an animal with discriminatory selectivity, flexibility, and planning capacity.

Edelman, along with other theorists, distinguished between 'primary' consciousness and 'higher-order' consciousness which in humans is associated with language, the temporally stable self, autobiographical memory, and the ability to imagine and plan for the future.

In the dynamic core hypothesis Edelman and colleagues (2000) propose that any particular conscious event combines a high level of information-rich discrimination and integration. The neural mechanisms of a conscious experience involves a functional cluster in the thalamocortical system, within which reentrant neuronal interactions yield a succession of unitary states. The boundaries of a dynamic core may change over time, with some neuronal groups leaving and others being incorporated.

According to Tononi and Edelman (2000), high values of a measure called 'neural complexity' (C) characterize conscious events. C reflects the extent to which the dynamics of a neural system are both integrated and differentiated. Modeling studies suggest that the thalamocortical system is suited to producing dynamics of high neural complexity.

Tononi has suggested that consciousness corresponds to the capacity of a neural system to integrate information, defined formally as combining a large repertoire of states, such as a visual experience of an object like a computer screen. This information-theoretical proposal is based on the notion that the occurrence of any conscious scene simultaneously rules out the occurrence of a vast number of alternatives and therefore constitutes a highly informative discrimination. Tononi has proposed a formal measure of the degree of consciousness that is enabled in a system. This measure, called phi, is defined as the amount of causally effective information that can be integrated across the weakest link of a system. According to the theory, consciousness as measured by phi is characterized as a disposition or potentiality. Both neural complexity and phi can be considered to measure the spatial aspect of the balance between differentiation and integration in a neural system.

Seth and colleagues (2006) have suggested useful additional measures of neural dynamics to measure other aspects of this balance, including complexity across time (temporal complexity) and across different levels of description (recursive complexity). Temporal complexity reflects the fact that consciousness extends over time in several ways. Many experiments suggest that it takes 100 ms for sensor stimuli to be incorporated into a conscious scene and that neuronal readiness potentials can appear several hundred milliseconds before the awareness of an intention to act. Recursive complexity reflects the fact that brains show rich organization at multiple levels, from molecular interactions within individual synapses to reentrant interactions among distinct brain regions. A combination of measures may be needed to adequately characterize the neural dynamics relevant to consciousness.

Edelman, Tononi, and Sporns have proposed that out of four potential connectivity patterns in the thalamocortical system (Figure 8.49) the one that enables conscious functions is the formal pattern shown on the right, called 'Complexity'. A purely random connectivity machine

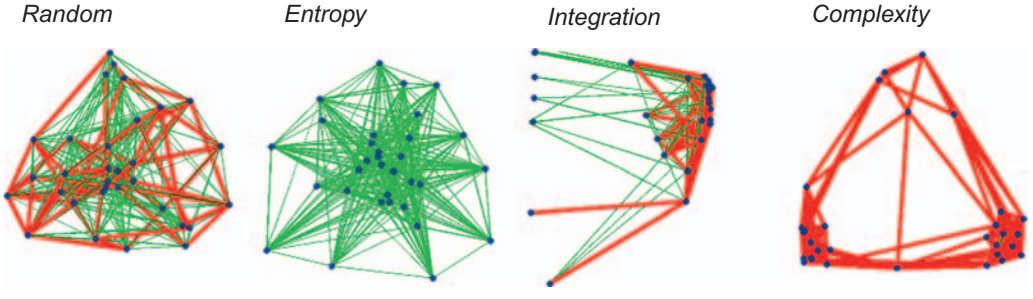


FIGURE 8.49 Four possible thalamocortical patterns of connectivity. In recent years we have seen progress in understanding the connectivity pattern of the core brain, the thalamocortical system. Some proposals about the conscious state and its contents make claims about the kind of dynamic connectivity that may be needed for a conscious brain. For example, they aim to answer why the cerebellum is not considered to support conscious contents, while the cerebral cortex and thalamus, in combination, are believed to do that. *Source*: Sporns and Tononi, 2002.

is unable to sustain specific contents; an entropy system loses information. The third connectivity pattern, integration, is very useful for specific biological functions, but fails to have the high level of flexibility that characterized conscious brain functions. Complexity is a formal measure that allows for high-dimensional discriminability between different inputs and outputs, and is also able to integrate very high numbers of such states in a unitary fashion. These proposals can be formalized, and have been tested against detailed models of the thalamocortical system, the cerebellum, and other parts of the brain (Izhikevich & Edelman, 2008).

6.3 Does consciousness require an experiencing self?

Intuitively most of us believe that conscious experiences involve an 'experiencing self' – a personal viewpoint on the world that may be supported by parietal and prefrontal areas of the cortex (Baars *et al*., 2005; see Chapter 12). In daily life we use phrases like 'I'm awake', 'I see the coffee cup', 'I lost consciousness', 'I couldn't control myself', and so on. However, there is a large philosophical literature that is critical of this commonsense idea. For many years the 'observing I' was ridiculed as 'the homunculus fallacy' (from the Latin word *homunculus*, meaning 'little man'). The problem, according to the critics, is that to make sense of the observing self, a little observer would have to sit in the brain, looking at the sensory inflow. But to make sense of the little observer inside the brain, it would *also* need a little observer inside, and so on *ad infinitum*. Such an infinite regress does not explain anything.

However, not all versions of an observing self lead to an infinite regression (Baars, 1988). It is possible to have an executive capability in the frontal and parietal lobes, one that is able to interpret information from the senses in terms that are important for decision-making – like: 'Is this news good for me? If not, will it hurt? How much? Should I run away? Or would I feel embarrassed if I did'? There is a great deal of evidence for an executive network in the human brain (Chapter 12).

The weight of scientific opinion may now be swinging back to the idea of an executive 'I'. The brain regions in the frontal lobe shown in Figure 8.50 are the same that were damaged in the classic case of Phineas Gage, and other frontal lobe patients who suffer from a radical change in personality and impaired self-control. The sense of agency in voluntary control is also dependent on the medial and lateral frontal regions, and the right parietal region (above) is a crucial area for 'perspective of the self' in the neurological condition of parietal neglect (Baars, 2002; Baars *et al*., 2003).

Is an 'I system' needed for conscious experiences? For that reason, this emerging literature may give us the first scientific handhold on these notoriously difficult questions.

The right PPC may be one of the brain areas that support 'the perspective of the self' and the sense of personal agency in action control. The posterior parietal

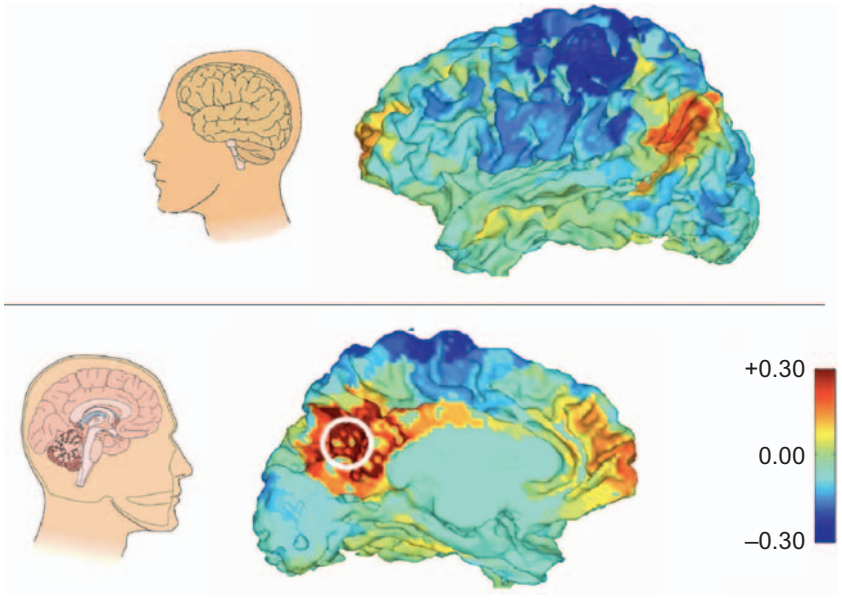


FIGURE 8.50 The precuneus/medial prefrontal region may support the 'self as observer'. Self-related regions of the brain are also high-traffic hubs, as indicated by mapping studies of the white matter – the major signaling hubs and highways of the cortex and thalamus. Brain connectivity follows 'small world' mathematics, both structurally and functionally, as measured by 'signal traffic flow'. *Source*: Hagmann *et al*., 2008.

cortex may also be involved in loss of consciousness due to anesthesia (Alkire & Tononi, 2008).

William James pointed out that the 'I as observer' is not the same as the 'me' as an *object* of perception and thought. That is, the 'I' is not the face you see in the mirror, nor is it the objectified concept of ourselves as others may see us. Rather, the 'I' is the point of view of the perceiver, the volitional actor and thinker. Of course it is quite possible that the 'I' is an inferred entity, and even one that is mythical, or culturally acquired. After all, human beings constantly make inferences about all kinds of nonexistent entities in the world, and the mere fact that we assert the existence of something does not prove that it does exist. However, the perspective of the 'I' seems to be universal across cultures and fundamental. Young children seem to have a sensorimotor perspective from very early on, and presumably an emotional one as well. Many of our emotions have to do with experiences of well-being and danger to the experiencing self. To feel hurt is equivalent to a negative evaluation of the experiencing self. Other emotions, like shame, guilt, and pride, are thought to be 'self-conscious emotions'; that is, feelings that reflect how we believe we are perceived in the social world.

6.4 Why are conscious events reportable?

Our basic evidence for the fact that others are conscious is what they tell us – which fortunately coincides with our own experience much of the time, at least in the perceptual world. But any scientific theory must ultimately also explain its own most basic evidence. So far, there are not many attempts to explain why it is that conscious events are reportable.

A somewhat trivial explanation is that the forward 'global broadcasting' of perceptual contents from sensory cortices to the frontoparietal regions also activates language areas, like Broca's area, which are needed to report conscious events. But that is not really good enough. People who are aphasic can still report conscious experiences, and even people who are paralyzed can make use of eye movements to fixate letters on a large keyboard display, to 'type' their conversations. The output modality of speech is not a necessary requirement for being conscious about events.

At a somewhat deeper level we may argue that perceptual objects and events can be pointed out, a skill that even very young children can use. Children and their caretakers constantly play the game of 'Look! There's a toy'! or later, 'Look! There's a (fill in the name)'. It is obviously an important part of our growing up to know the shared social and interpersonal reality of objects, events, and people. In basic cognitive terms, it may be that consciousness has a close relationship to what linguists call *deixis*, the realm of things that can be 'pointed to'. A number of linguistic expressions serve the process of deixis, which may be a fundamental aspect of human socially shared reality. Deixis includes the perceptual world, but also the social world, even the shared imagining of a nonvisible world. Children can talk about Santa Claus and the tooth fairy in conventional ways.

Philosophically, consciousness may have a role in objectification – creating a world of entities that have known or agreed-on properties, and that persist over time. It is significant that the dorsal stream of the visual cortex does not directly lead to conscious outcomes even though it is essential for both spatial localization of the self and for actions like reaching. Therefore it is not the case that all visual events can be objectified, or that they can necessarily become objects of consciousness. Indeed, we can make the case that it is important that the dorsal and ventral visual stream must be dissociated from each other in order to prevent interference between temporally precise visuomotor actions.

Objectification – turning events into stable objects of perception or thought – is also a crucial part of human thinking. Humans routinely commit the logical fallacy of reification, turning an abstraction like 'democracy' into a hypostatized entity. That mental process has its uses, but it can also be misleading. We also routinely freeze dynamic events, like aspects of economics, biology, or physics, which might be dealt with more accurately with mathematical tools for dealing with fast-changing entities. Newtonian calculus was invented precisely to describe dynamic events that can be labeled by words in only a very impoverished fashion. Since the invention of calculus, numerous mathematical advances have made it possible to measure and describe dynamical systems (like the brain) with greater accuracy. However, human language and perception have not kept pace. We still talk about 'the economy' or 'the brain' in essentially static terms.

It is at least possible that excessive reification reflects our conscious style of perceiving and thinking about the world. We may be biologically condemned to 'ventral stream thinking', in spite of the fact that our mathematics are able to deal with a more dynamic world than most of us do on a daily basis.

These questions are becoming answerable in cognitive neuroscience. It is important therefore to ask them as clearly as we can, and not to take the reportability of conscious events for granted.

6.5 Evidence for unusual states

The three main states of the daily cycle may give us a better basis for thinking about unusual states – drug-induced, disordered, or states of mind that may be reached after years of training, such as meditation or yoga. Human history and literature contain numerous descriptions of extraordinary states of mind, but scientists set high standards for extraordinary claims. Some methods, like neurofeedback and hypnosis, are known to have robust effects, but we still need to know much more about their brain bases and results. It is possible to err on the side of too much skepticism as well as too much credulity; good scientists aim to be open-minded, but still look for very strong evidence.

Some mystical experiences traditionally are associated with epilepsy, as in the famous case of Fyodor Dostoyevsky, who suffered from epilepsy and described powerful mystical 'auras' before seizures. Indeed the first book on epilepsy was attributed to the Greek physician Hippocrates (fourth to fifth century BC), titled, *On The Sacred Disease.* Epileptic patients commonly describe altered states of consciousness in association with EEG hypersynchrony, even without overt seizures (Figure 8.5). Most of those altered states are experienced as unpleasant. Since hypersychrony alters the workings of the thalamocortical core, there could well be a link between altered subjective states and brain rhythms.

Psychedelic drug effects have been compared to waking dreams, often showing vivid visual hallucinations, delusional beliefs, dream-like actions, intense emotional encounters, difficulty keeping track of time, and sharp discontinuities from 'scene' to 'scene'. Similar experiences are described with a variety of psychoactive drugs, including LSD, cannabis, and traditional plant preparations like ayahuasca. There is a structural resemblance between the LSD molecule and the major neuromodulator serotonin, which is known to be involved in REM dreaming. However, the link between psychedelics and normal dreaming is still speculative.

Delusions and hallucinations are defining symptoms of psychosis, which can be very harmful indeed. Typically the first episode of schizophrenic disorder occurs in late adolescence or early adulthood, often a period of major life change and stress. It is believed that marijuana use may expose some vulnerable individuals to a higher risk of developing schizophrenia. However, in spite of decades of research, schizophrenia continues to be an unsolved puzzle.

One major difference between psychosis and recreational use of psychedelics is the degree to which highly unusual experiences are desired or not. 'Recreational drugs' by definition are taken with the goal of having unusual experiences. In the psychoses, delusions and hallucinations are often extremely upsetting, frightening, and unwanted. They occur at unexpected times, interfere with normal life, and can develop into painful persecutory voices and distressing beliefs about oneself. They may be chronic. The degree to which these experiences are unwanted is one major difference between psychedelic drugs and dysfunctional psychotic experiences. By analogy, some people enjoy parachuting from airplanes or high suspension bridges. At the right time and place, they do those things for pleasure. If they were forced to do them against their will, and in a way that feels out of control, the same experiences might well be shocking and traumatic. Mental disorders are not a matter of choice, and people who suffer from them cannot stop at will.

In contrast, certain extraordinary experiences have been actively pursued over thousands of years. To experience altered states humans have used a huge variety of methods, including psychoactive plants, long fasting, alcohol intoxication, years of physical and mental exercises, visualization methods, deliberate disorientation, high altitudes, hypoxia, self-mutilation, intense sexual practices, dramatic settings and rites, lucid dreaming, rhythmic dancing, whirling, chanting and music, hypnotic suggestion, dissociative traumas, sleep deprivation, and social isolation. Many of these practices are no better understood today than they were centuries ago. Traditions like Buddhism and Vedanta Hinduism believe that humans can and should change their states of consciousness and their sense of self. That belief can be found in many times and places.

Self-reports about altered states are not persuasive to skeptics. Simply asking people whether some practice make them happier or more relaxed does not make for convincing evidence. Sugar pills can also lead to glowing testimonials. Indeed, there is hardly any practice that does not produce enthusiastic endorsements from believers. This is not to dismiss what may be truthful accounts by sincere and insightful practitioners. It is simply that unverifiable reports about private experiences have not led to cumulative progress in science.

Brain evidence about unusual states may be more convincing to skeptics because people cannot control their brain states at will. We cannot alter our EEG or fMRI scans to prove a favorite hypothesis. Obviously some psychological tasks are also resistant to personal biases. But the vast majority of studies of meditation and related techniques are seriously weakened by self-report biases. These results are rarely believed by scientific skeptics.

6.5.1 *Hypnosis, conversion disorder, and brainwave entrainment*

About one-fourth of the normal population is highly hypnotizable, as assessed by a standard hypnotic induction procedure. Hypnotic suggestions can change brain events, as in reducing the event-related potential (ERP) in response to a flashing light simply by 'hallucinating' a cardboard box covering the light (Spiegel, 2003). We do not know why hypnotic induction is effective in so many normal people. About 5% of the population are said to be 'hypnotic prodigies', who can hallucinate perceptual events, such as the buzzing of a fly; they can also enter into apparently dissociated personality states (Hilgard, 1974). fMRI studies show that hypnotically suggested pseudo-pain activates some of the same brain regions as real pain, and on the positive side, that hypnotic procedures can alleviate pain in chronic pain patients who have no other recourse (Spiegel, 2003).

The brain correlates of hypnosis itself may finally be coming into focus. For two centuries scientific students of hypnosis have known that hypnotizable individuals may experience a mild sense of loss of control over their voluntary movements. One common hypnotic induction method is to tell subjects to allow their arms to float upward freely. Good hypnotic subjects let that happen without discomfort. It is possible therefore that hypnosis may involve a functional dissociation between the part of the brain that's involved in voluntary control (such as the dorsolateral prefrontal cortex, DL-PFC) and the ability to monitor cognitive conflict (the anterior cingulated cortex, ACC).

Egner *et al*. (2005) reported in an fMRI-EEG study of hypnosis in the Stroop task that 'hypnosis decouples cognitive control from conflict monitoring processes of the frontal lobe'. Along similar lines, Faymonville *et al*. (2006) reported a widespread network of activations associated with hypnosis, but a relative *deactivation* of the precuneus, a brain region that is believed to be involved with the perspective of the self. That result might be consistent with a dissociation between self-control and self-monitoring during hypnosis, especially in highly hypnotizable subjects.

We are also seeing a scientific return to the topic of conversion disorder, called *hysteria* in medical history. In conversion disorders people experience 'psychogenic' analgesia, hyperalgesia, imagined symptoms of medical disorders, paralysis of the hands or arms, and the like, all in the absence of identifiable nerve damage. Because conversion symptoms were found to be changeable and responsive to suggestion, nineteenth century physicians proposed that the problem was due to autosuggestion. That is still a viable hypothesis, although it does not follow necessarily that conversion symptoms can be *treated* by suggestion.

Mild conversion-like symptoms are extremely common. Medical students who are first being exposed to the physiological details of serious diseases often become worried when they seem to notice 'real' symptoms in themselves. That 'medical student syndrome' is very common and it generally fades over time. It is possible that conversion disorders are a more lasting and disabling version of the general human tendency toward autosuggestion. The placebo effect is a positive version of the same phenomenon.

The 'hysteria' diagnosis has been strongly criticized in part because it was thought to be limited to women. However, nineteenth century physicians like Jean-Paul Charcot and Pierre Janet emphasized their findings that men showed conversion symptoms, especially after severe trauma like a railroad accident. Nevertheless, the very concept of conversion disorder lost popularity for decades. In recent years carefully controlled brain imaging studies have revived interest; there really is a patient population that suffers from these problems, which can be very painful and disabling (Cojan *et al*., 2009). Getting a clear diagnosis is a step forward, to distinguish conversion impairment from genuine brain damage.

6.5.2 *Neurofeedback*

Neurofeedback is defined as learning to control brain events by giving sensory (conscious) feedback, contingent on some brain event. In the animal literature it is often described as 'operant conditioning', which is really an experimental procedure rather than an explanatory framework. Neurofeedback is one kind of biofeedback training, which also includes training of peripheral events like increasing the warmth of a finger. Simply by holding a thermometer showing small changes in finger temperature one can learn to increase peripheral warmth, for example, which seems to help people relax and lower blood pressure.

Biofeedback studies of animals, using operant conditioning, have shown positive results over several decades. Animals with implanted electrodes can be trained to increase the activity of single neurons, and of larger populations of neurons. When justified for medical reasons similar training effects can be shown in humans. It is important just to stop and consider what a remarkable result that is. In a brain with billions of neurons, simple sensory feedback can allow training of voluntary control over otherwise entirely involuntary neuronal firing and other brain events.

However, neurofeedback training for specific brain oscillations, for example, may not result in enhancement of the targeted event. Surprisingly, even 'alpha neurofeeback training', for example, does not necessarily result in proven increments in alpha wave activity. This is a disconnect in the literature, which has mostly focused on testing practical outcomes. Oddly enough, the 'feedback' aspect of neurofeedback is sometimes lost.

This becomes less of a paradox if we consider that brain rhythms are under precise homeostatic control (John, 2002). If neurofeedback works, it is not just flipping a light switch in the brain; rather, we are jumping up and down on a large rubber boat floating on a lake. Our jumping causes real changes, but the brain still stays afloat – which is a very good thing. The brain is complex, dynamic, and multistable. That is how living systems can survive over many kinds altered environments.

We therefore have two separate questions:

- Does brain feedback show results? After many years of study the answer seems to be a very clear 'yes'. Figure 8.51 shows an example of fMRI feedback effects in chronic pain patients.
- Does neurofeedback have a simple, direct effect on the brain, or does it have both direct and indirect effects? The evidence seems to favor the latter, including important positive effects in conditions like ADHD, epilepsy, depression, and perhaps others (Gruzelier, 2008) (Figure 8.52).

A large number of studies of EEG neurofeedback show significant results, but long-term studies are still often lacking. Because neurofeedback may work in cases where other medical treatments have failed (as in depression and epilepsy), long-term trials would seem to be vitally important.

6.5.3 *Sensorimotor rhythm (SMR), alpha/theta feedback, and other trained oscillations*

Sterman and Egner (2006) describe evidence that 'neurofeedback treatment of epilepsy/seizure disorders constitutes a well-founded and viable alternative to anticonvulsant pharmacotherapy'. That is important both medically and scientifically. Drug treatments for epilepsy do not always work, and having another treatment modality available is helpful for many patients. Scientifically, because epilepsy (which can have many different causes) manifests as slow EEG hypersychrony, the ability to modify seizure activity in the brain tells us something important about the role of brain rhythms and their voluntary control.

What is the SMR, the sensorimotor response? SMR was discovered in EEG studies of cats that were taught to suppress a previously learned and reinforced response. These animals shows a transient, alpha-like EEG rhythm in the sensorimotor cortex. 'This rhythm was characterized by a frequency of 12–20 Hz, not unlike EEG sleep spindles, with a spectral peak around 12–14 Hz (Roth *et al.*, 1967). The investigators decided to study this distinct rhythm directly, attempting to apply the operant conditioning method to see if cats could be trained to voluntarily produce SMR, by making a food reward contingent on SMR production. Cats easily accomplished this feat of EEG self-regulation, and the behavior associated with SMR was one of corporal immobility, with SMR bursts regularly preceded by a drop in muscle tone. When the Sterman laboratory was commissioned to study the effects of an epilepsy-producing drug, they happened to discover that SMR-trained cats were less susceptible to the chemically induced seizures. This effect generalized to humans. Intracranial studies in animals showed that the SMR comes from the ventrobasal nuclei of the

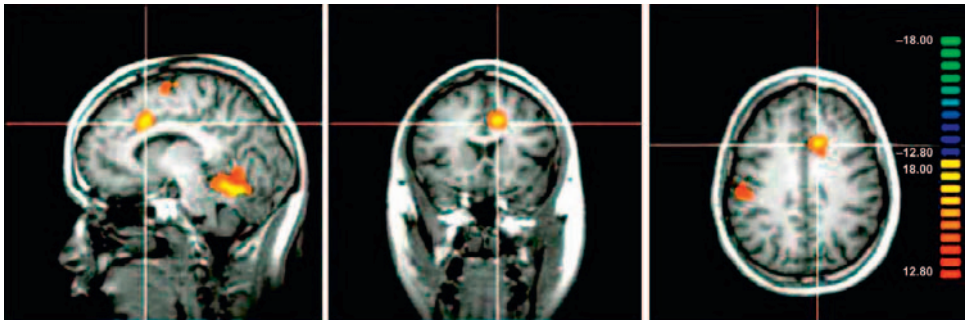


FIGURE 8.51 Local brain activity controlled by fMRI feedback. Local brain activity increases after feedback training for fMRI activity in chronic pain patients. The training target was activity in the rostral anterior cingulate cortex, which is known to be involved in pain perception (rACC). *Source*: deCharms *et al.*, 2005.

thalamus, and that it has a major role to play in inhibition of unwanted responses.

SMR feedback has now been shown to be an effective treatment in cases of human epilepsy, ADHD, and impulse control disorder (Sterman, 2006). It is therefore a potential treatment. Thus SMR is one of the rare cases (so far) where neurofeedback has resulted in a thorough psychobiological understanding of an important medical condition. With improved brain recording methods we can expect to see more of such encouraging results. (Similar findings have been reported with another endogenous brain oscillation, the 'Slow Cortical Potential'.)

According to Sterman (2006) the American Academy of Child and Adolescent Psychiatry considers neurofeedback for seizure disorders to meet criteria for 'Clinical Guidelines' of evidence- based treatments '…these results have been achieved in an extremely difficult subgroup of epilepsy patients, those with poorly controlled seizures who had proven unresponsive to pharmacological treatment. On average 80% of patients trained at enhancing SMR amplitudes were shown to display significant clinical improvements'. (Kaplan, 1975; Seifert & Lubar, 1975; Sterman, MacDonald, & Stone, 1974)

It is worth pointing out that neurofeedback is inherently still mysterious in that we do not understand the role of conscious feedback in enabling voluntary control of thalamcortical waveforms. That reflects our current limitations. SMR represents an outstanding example of solid scientific foundations enabling important advances in treating serious disorders. It would seem to be especially important to study SMR for attentional deficits and impulse-control disorders, which are often difficult to treat.

6.5.4 *Rhythmic entrainment of brain waves*

If brain rhythms constitute one basic code for neural signaling, it would be interesting to know if we could drive them externally. Brain wave entrainment has been described with TMS (transcranial magnetic stimulation) and tACS (transcranial alternating current). In neurosurgery direct electrical stimulation of the cortex has been used for half a century. (See Chapter 1, and earlier in this chapter.) It might also be possible to use auditory, visual, or motor rhythms. However, although there are many popular claims about the effects of auditory entrainment, they have not been demonstrated to work by appropriate medical and scientific standards so far.

Ideally, an external sensory driver for brain waves would have to be aimed at the right part of the brain, at the right rhythm, and to be started and stopped at the right time. There are still many unanswered questions about endogenous brain rhythms and how they interact with external inputs. As we have mentioned, visual stimulus detection is better at the peak of the alpha wave than at the trough (Vanrullen & Koch, 2003). That may be only the first example of how the ongoing activity of the brain shapes input processing. The brain is always active, and sensory input modulates only ongoing activities.

Neurofeedback and techniques like acupuncture also have been studied in animals, thereby ruling out placebo effects. But so far, what seem to be promising methods have not been widely applied. We now understand more about brain oscillations, for example, which gives us a better rationale for neurofeedback training. But we are just beginning to understand the details. It is worth noting that neurofeedback training always involves a *conscious* feedback signal (Baars, 2002).

Hypofrontality – decreased metabolism in the frontal lobes may be a common theme for altered states. Dietrich (2002) argues that lowered frontal metabolism is a shared feature of hypnotizability, 'runner's high', 'flow', and other unusual states of mind. Low frontal metabolism also occurs in simple drowsiness and other semiconscious states, as in emerging from general anesthesia. 'Grogginess' is a commonsense term for the state in which we are awake but not very

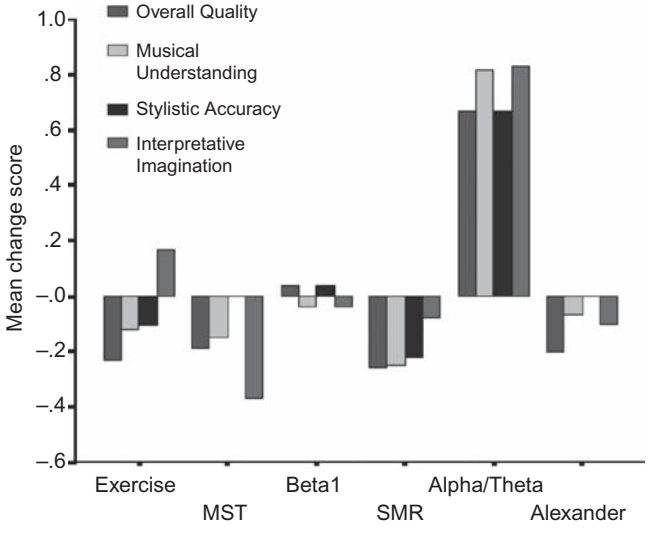


FIGURE 8.52 Alpha/theta training improves high-level musical and dance performance. Gruzelier (2008) has shown that 20 neurofeedback training sessions designed to increase alpha and theta activity had marked effects on performance in conservatoire musicians and dancers. Evaluation was by independent judges who were blind to the treatment conditions. Neurofeedback training (NFT) showed improvements equivalent to two conservatoire grades, while other treatments showed no difference. Technical skill levels did not improve, but musicality, conviction, stage presence, and relaxation were improved.

alert, and executive functions may seem impaired. Obviously not all these states are the same. Low frontal metabolism may be one overlapping feature.

6.5.5 *Meditation and similar practices*

Meditation is often described as a state of relaxed alertness. The term 'meditation' covers a host of mental techniques with possibly different effects, but one common method is silent repetition of a word called a mantra. There is unresolved debate whether the mantra can be any arbitrary sound or not. Mantra meditation is described as a method for changing mind states, as taught in Asian traditions like Vedanta, Buddhism, and traditional Chinese medicine. It has also been widely practiced in European and Middle Eastern traditions. Because it is so simple (no equipment required) it is almost sure to have been tried in many times and places, not excluding hunter-gatherers, who often have elaborate shamanistic initiations and practices.

A different procedure is called 'mindfulness meditation', described as '… allowing any thoughts, feelings, or sensations to arise while maintaining a specific attentional stance: awareness of the phenomenal field as an attentive and nonattached observer without judgment or analysis' (Cahn & Polich, 2006, 2009). These two techniques are the best-studied ones so far, with hundreds of articles in peer-reviewed journals. They may differ in the degree to which they encourage free-floating attention versus focused concentration on a single mental content. Over several decades, meditation methods often have been reported to increase brain activity and coherence (phase-locking), especially in the theta, alpha, and the beta-to-lower-gamma band of the EEG. Frontal-lobe interhemispheric coherence is also reported, as well as improved attentional functioning (Lazar *et al*., 2000; Lutz *et al*., 2004; Tang *et al*., 2007).

One of the surprises with simple mantra repetition is a significant drop in metabolic activity, even in new practitioners, as reflected in 'breath suspensions' – spontaneous stopping of the breath, but without compensatory breathing afterward (Figure 8.53). This is different from holding our breath voluntarily. In swimming, for example, we may take a deep breath before diving and then feel the need to take some extra breaths after coming up for air. Normal breathing is under tight homeostatic control, and voluntary breath-holding requires compensatory breathing, to make up for decreased oxygen. Therefore the finding of spontaneous, uninstructed breath suspension without compensatory breathing is a genuine surprise. It does not occur in normal resting controls. The lack of compensatory breathing suggests that energy demand has indeed dropped more than an ordinary resting state, as has been demonstrated by measuring O_2/CO_2 exchange (Benson *et al*., 1975; Hoffman *et al*., 1982).

Herbert Benson and colleagues have proposed that these results represent a 'relaxation response', on the analogy with other physiological reflexes. The

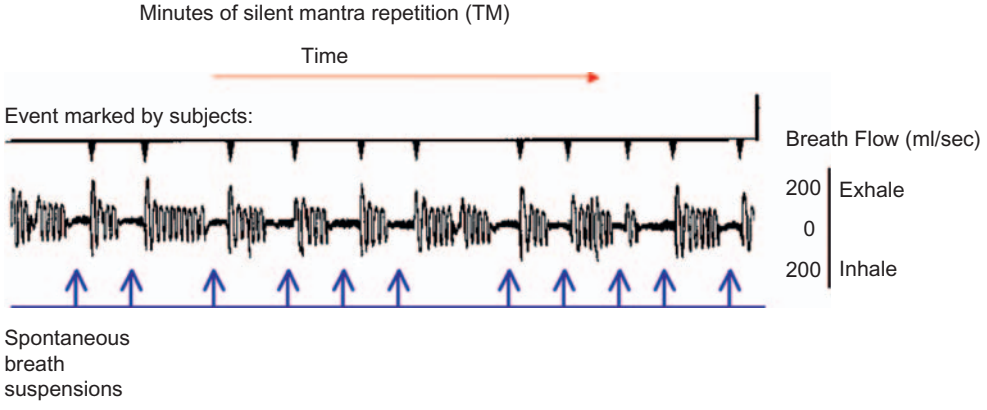


FIGURE 8.53 Spontaneous breath suspension in mantra repetition. Repeated, spontaneous breath suspension in silent mantra repetition coincides with subjects' reports of 'pure conscious' experiences. Breath suspensions occur without compensatory overbreathing, different from voluntary breath-holding, which tends to be followed by compensatory breathing. Breath suspensions are said to signal moments of 'pure consciousness', defined as clear conscious moments without content. These conscious moments are the purpose of the technique. This study was performed on practitioners of Transcendental Meditation, a silent mantra technique from the Vedanta tradition in India. However, similar phenomena may occur with the use of arbitrary mantras. Figure adapted from Benson *et al*., 1975, and Hoffman *et al*., 1982.

parasympathetic nervous system is involved with relaxation (in competition with the sympathetic nervous system) and it is plausible that there could be a way of evoking a parasympathetic 'switch', for restoring physiological and mental resources. However, many other variables coincide with the effects of mantra meditation, and it is puzzling why mere mental word repetition would evoke such a pervasive physiological and brain response. What is perhaps most important about the rapid physiological effects of mantra meditation is that is tells us there is something surprising and different about such a simple practice. The apparent metabolic drop also casts a different light on the brain wave results that are reported to go along with it.

Spontaneous breath suspensions are also reported to be associated with reports of periods of 'pure consciousness', defined as relaxed alertness without any specific mental contents. The aim of mantra meditation is to produce 'pure consciousness' experiences until they become habitual and are integrated with daily life. These effects have been described with novices and advanced practitioners, and also with the use of arbitrary mantras as in the Relaxation Response. Converging evidence has come from measures of metabolism, sympathetic nervous system tone, and recently, very large-scale changes in gene expression. Because the exact functions of 'relaxation-related' genes are not yet clear, this promising direction requires additional studies (Jacobs *et al*., 1996; Dusek *et al*., 2006).

What brain changes take place after many years of pursuing these practices? EEG studies of advanced meditators have shown high levels of gamma, alpha, and theta synchrony (e.g. Lutz *et al*., 2005). These studies commonly focus on highly trained individuals. For example, Lutz and colleagues studied four advanced meditators with 15,000 to 45,000 hours of training. Advanced practitioners must be different in many ways. They may resemble top athletes, dancers, or musicians, who may begin early in life with exceptional talents and predilections. The result it essentially like asking why Tiger Woods is an outstanding athlete. That question is inherently difficult, because we would have to start from childhood with control subjects, and do longitudinal studies over years, only to end up with a single case history.

Nevertheless, it is still interesting when measurable brain changes can be observed over half an hour of meditation, even among exceptional individuals. Broca and Wernicke used very small numbers of rare subjects to discover the language areas of the cortex in the nineteenth century (Chapter 1). Intensive study of a few patients also led to major progress in understanding the hippocampus in memory (Chapter 1). There are good precedents for focusing on small numbers of exceptional individuals, as long as the evidence cannot be influenced by biases and expectations.

However, it is almost impossible to find control groups that are comparable to advanced practitioners. As a result, it is difficult to know how well these results generalize to a wider population. The answer to that question historically is that over time, the generality of the findings can be tested in other ways. Broca's area is really involved in speech production, as we can now tell in dozens of different ways, and with tens of thousands of human subjects. But it all started with careful studies of a single patient. The case of HM demonstrates even better methodology, because this surgically lesioned man was studied over decades by many different laboratories. That ensured that different researchers were all dealing with the same human being. However, that kind of coordination has not yet been achieved in studies of altered states. As a result, we have numerous articles on what may be vastly different advanced practitioners.

High interregional coupling in the theta-alpha range is suggested as an explanation for meditation states (Hebert, 2005). Advanced practitioners of meditation and similar training techniques may describe states of high tranquility, consciousness without specific contents, expansion of subjective space, consciousness during sleep, and the like. Researchers are only beginning to seriously address the subjective experiences of advanced practitioners, which is after all what motivates meditators to do what they do.

As a result, even after four decades of studies, we do not know nearly as much about meditation effects as we would like. By comparison the neurofeedback literature is in somewhat better shape, although it, too, still has numerous gaps. None of this research literature is entirely satisfactory; none has been studied quite as much as we might like. One hopeful sign is a better understanding of EEG rhythms in specific brain locations, identified with fMRI. Brain rhythms historically have been merely understood as correlates of *something* interesting, with no understanding of what exact role they might play. High alpha coherence is a little like knowing that people have heartbeats, but without understanding the role of blood circulation and the heart's pumping action. Fortunately the lonesome tree of uninterpreted brain rhythms is now being enriched by a young forest of related facts and plausible functions. Improved understanding allows us to make better sense of the brain correlates of meditation and similar practices.

6.5.6 *Out of body experiences can be induced by brain stimulation*

Some of the most reliable results come from studies of 'out of body' experiences (OBEs). Seeming to look at one's body from the outside certainly counts as extraordinary. On this topic there has been genuine progress. We now know, for example, that direct stimulation of the right posterior parietal cortex (PPC) can evoke dramatic changes in experienced body space (Figure 8.54). Some epileptics experience major alterations in body space, perhaps because of hypersynchronous activity affecting this region. Damage to the right PPC is also known to produce alterations in body space. Parietal neglect is a well-described disorder that leads to radical alterations in perceived space.

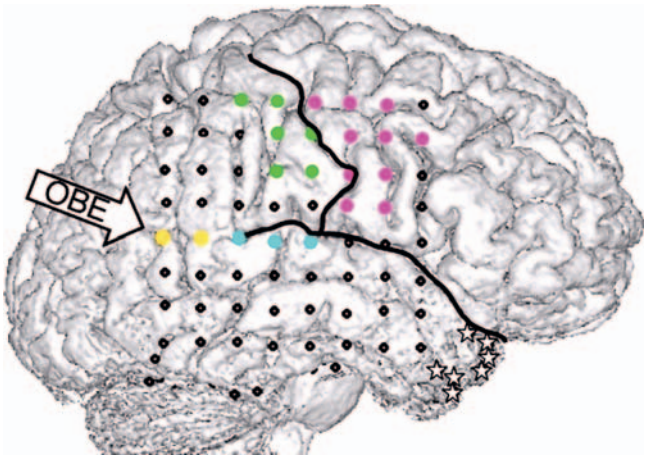


FIGURE 8.54 The right parietal cortex and out-of-body experiences. Tong (2003) after Blanke (2002).

Indeed, the parietal cortex has emerged as a player in a number of unusual experiences. It seems that we can begin to see a growing body of evidence that bears on at least this one kind of extraordinary experience.

7.0 SUMMARY

Much territory has been covered in this chapter. The good news is that we are getting a better understanding of consciousness and attention. There is even a major simplification of the evidence, as the pieces of the puzzle start to come together.

Attention and consciousness can be considered as complementary processes (see Figure 8.55). Conscious contents often are thought to involve the widespread distribution of focal contents, like the sight of a rabbit. As soon as we see a rabbit (consciously), we can also judge whether it's real, if it's somebody's pet, we can laugh or scream for fear of being bitten, and try to remember if rabbits carry rabies. The point is that a great variety of brain events can be evoked by a conscious object, including a great variety of unconscious processes. Conversely, we can focus cognitive resources on any topic to which we decide to devote attention, such as the contents of this book. In order to learn, we direct attention to a topic over and over again, with the result that we have many different moments of consciousness, each one able to evoke additional cognitive processes, as needed. Learning a difficult subject involves allocating attentional resources over time.

Consciousness typically involves a small amount of content at any given moment, like the sight of a rose

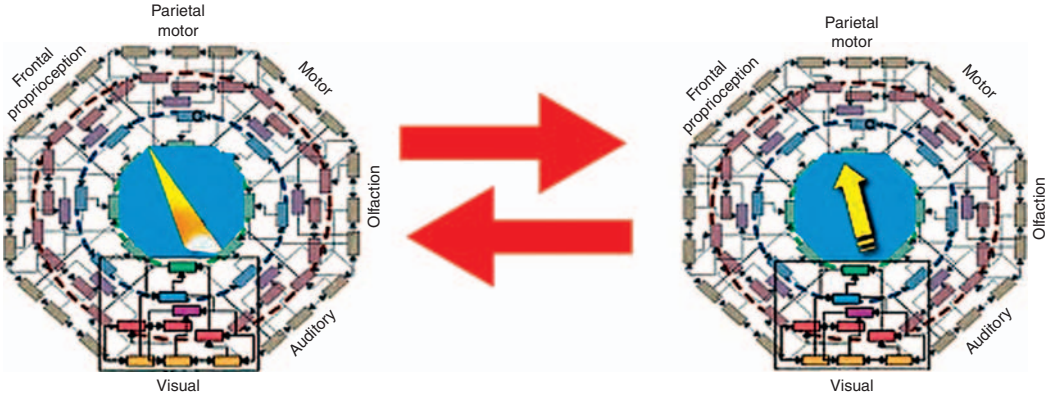


FIGURE 8.55 Attention and consciousness. Attention often is thought of by analogy to a spotlight, moving to 'point at' and select some part of the world for conscious processing. Controlling the 'spotlight of attention' requires frontal and parietal cortex as well as subcortical regions. Recent evidence suggests that perceptual consciousness may activate cortical regions in the opposite direction, beginning from primary sensory cortex (posterior) and activating more frontal regions. Thus we can think of two streams of interacting information flowing back and forth in the cortex, one *selective* (selective attention), and the other *integrative and distributive* in its effects (perceptual consciousness). *Source*: Baars & Fu, 2007.

bush, which may recruit and mobilize many unconscious brain functions. In attention, major functions like motivation, planning, emotional needs, and the like, become directed to a specific object in the world. Voluntary attention particularly requires the recruitment of frontal lobe resources toward acquiring new and better information on behalf of some explicit goal or task. Frontoparietal regions of cortex may then enhance processing in visual regions (for example) in order to sharpen, clarify, and make conscious some part of the visual world. Episodic and declarative learning seem to occur automatically as a function of conscious contents, which in turn may be guided by voluntary attention. The three major thalamocortical brain states of the circadian cycle show different operating styles of the attention-consciousness dialogue. A major function of slow-wave sleep and REM dreams is to consolidate the memory of events that were initially perceived and learned in the waking state.

Understanding the brain basis of consciousness and attention is still a formidable challenge. Some hints come from Table 8.4, describing what the brain is doing in the three basic states. Notice the role of neuromodulation, chemicals spread by small numbers of neurons located in basal nuclei, which project their axons to higher parts of the brain. The thalamus also plays an essential role in the three major states. However, the *contents* of consciousness are believed to be largely controlled by the cortex.

TABLE 8.4 Brain activity in waking, dreaming, and sleep

Thalamocortical operating mode	Raw EEG (Surface electromagnetic field)	Neurons and their interactions	Other features
Waking consciousness			
People report normal conscious experiences, can carry out standard cognitive tasks, and exercise voluntary (executive) control over their skeletal muscles.	Fast, low-amplitude, irregular waveforms, which appear to contain many different frequency bands. Some highly synchronized activities may be happening even while the surface EEG looks mixed.	Highly active and interactive with other thalamic and cortical neurons.	Free flowing sensory input and motor output, with limited-capacity competition for conscious and executive events. Active problem-solving and learning. Conscious episodes are automatically encoded in memory by the hippocampal complex and neocortex. Some episodic memory consolidation may occur during waking, but mostly in sleep.
REM dreaming			
When questioned, reported as conscious.	Fast, low-amplitude, irregular waveforms, which appear to contain many different frequency bands. Some highly synchronized activities may be happening even while the surface EEG looks mixed.	Active, highly interactive with other thalamic and cortical neurons.	Blocked sensory input and motor output. Conscious contents are internally generated. Tacit problem-solving may occur. It is believed that implicit and procedural memories may be consolidation in the REM state.
Sleep stages 1–4			
Arousability goes down from stage 1–4, and less mentation is reported. However, some mental activity is reported even from deep sleep.	As arousability goes down, there is an increasing number of slow, high-amplitude, regular waves.	Massive 'buzz-pause' activity in near unison in the thalamocortical system. The simultaneous 'buzz' activity (the Up State) allows for waking-like interactivity. The 'pause' or Down State blocks signaling between cells.	Blocked sensory input and motor output. Recent episodic memories are replayed in the hippocampal-neocortical system during the Up States of the slow-wave rhythm, and explicit memory consolidation occurs.
Epileptic loss of consciousnes			
	Slow, high-amplitude, spike-shaped, regular. May originate in the hippocampus and temporal lobe, though other sources have been reported.	Massive 'buzz-pause' activity in near unison, thalamic and cortical. Hypersynchronous activity is thought to recruit expanding areas of cortex.	Lost functions, including consciousness, may be partial or complete. Automatic actions may occur, resembling sleepwalking.

Table 8.4 summarizes the major features of the three daily states of consciousness. Notice that the brain activity (although most important) is not the only aspect of sleep and waking states. Prominently the sensory input and motor output is blocked during REM dreaming (to prevent us from acting out our dreams) and during slow-wave sleep. In some REM sleep disorders, motor inhibition at the spinal cord is released, with the result that people may act out hallucinatory or delusional behaviors in a semiconscious way. Some sources suggest that thalamocortical disruption of the normal rhythmic cycle may be involved in serious brain disorders like psychosis.

The slow wave of sleep can be decomposed into an 'Up State' (the peak of the slow wave) and a 'Down State' (the trough). The Up State allows neurons to fire at their normal waking rates, and to interact with each other for a second or less. The Down State blocks these activities. Thus, some scientists have suggested that we may actually be awake about one second at a time during SWS (slow-wave sleep). When we look at the arousal threshold on this second-to-second scale, therefore, the arousal threshold may in fact oscillate quickly back and forth.

Like the waves in the ocean, signal propagation in the brain is a mix of many different waves. Alpha waves were the first to be observed, because they are so easily spotted: They appear in the raw EEG above the occipital cortex when the eyes are closed in a relaxed state. When the eyes are opened, alpha typically is interrupted by faster, irregular, low-amplitude EEG, labeled beta and gamma. However, complex waveforms can be decomposed into separate wave bands. These have now extended into well up to 200 Hz, sometimes 1000 Hz.The conventional range for gamma is still taken to be 30 to 120 Hz, but it is safer just to use numbers. Our verbal labels for brain rhythms are arbitrary and likely to change.

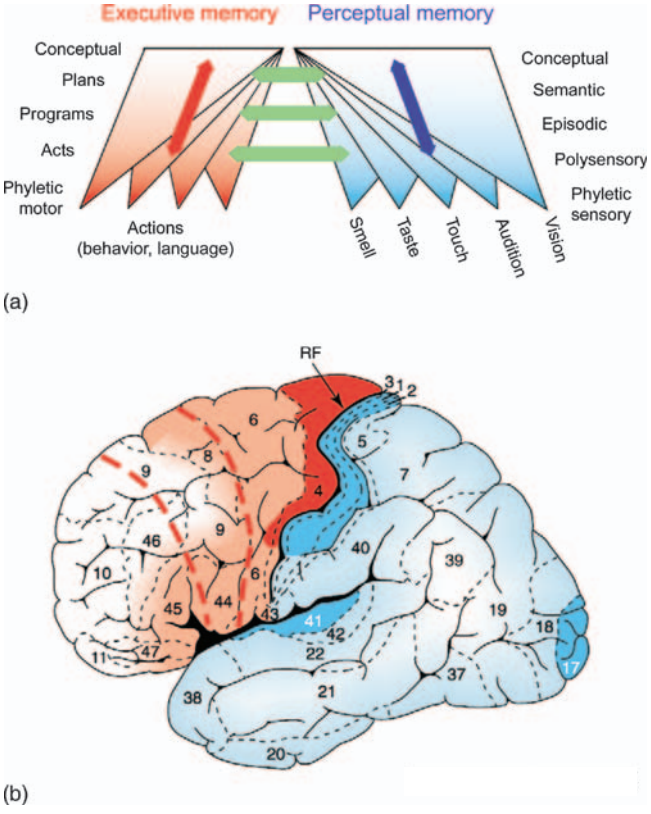
Waveforms in the brain interact. Waking rhythms may add, subtract, synchronize, desynchronize, phase lock, and multiplex. Slower waves may carry (multiplex) faster waves. It has been suggested that the very slow oscillations (0.1–0.5 Hz), delta (0.5–3 Hz), theta (4–7 Hz), alpha (8–12), beta (13–29), and gamma (30–120) all may be multiplexed under some conditions. Certainly theta commonly carries gamma activity, and the Up State of the delta wave during slow-wave sleep involves waking-like complex, interactive, high-frequency activity.

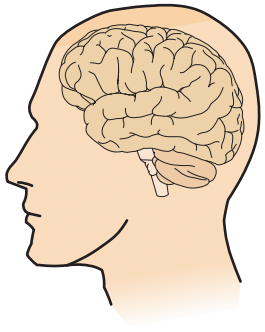
8.0 STUDY QUESTIONS

1. What major brain structures are involved in maintaining conscious waking, deep sleep (slow-wave sleep), and REM dreams? How do we switch between states?
2. What is the best-established function of slow-wave sleep? Of waking? Of REM dreaming? (If no function is established, just say so.)
3. When you learn to ride a bicycle really well, what happens to your cortical activity for sensorimotor control?
4. How can two brain areas that represent the visual field be coordinated?
5. What is meant by multiplexing of brain waves? What might be an example?
6. What are the main effects of selective attention? What part of the brain appears to control purposeful attention?
7. What's meant by 'the architecture of sleep'? Describe some of its features and timing.
8. What are some hypotheses about REM dreams? What kind of function might it have? How widely is REM dreaming distributed in the animal kingdom?
9. What are the basic functional and electrophysiological features of the conscious waking state? What kind of cortical waveforms seem to occur during conscious waking?
10. Describe the Up and Down States of slow oscillations.
11. Describe neurofeedback training. What is it useful for?
12. Is there convincing evidence that hypnosis reflects a genuine brain state?
13. What are the pros and cons of surface (scalp) EEG compared to intracranial EEG (iEEG)?
14. Meditation methods have been described for thousands of years. What are some commonly cited features? What evidence do we have pro or con?

What sort of life (if any), what sort of world, what sort of self, can be preserved in a man who has lost the greater part of his memory and, with this, his past, and his moorings in time?

Oliver Sacks (1995)





How memory might be encoded in many parts of cortex. The neuroscientist Joaquin Fuster's conception of long-term memory traces encoded in cortex. Posterior cortex has more perceptual varieties of stored traces, while the frontal lobe has executive and action-related traces. The principle is believed to be that neocortex (the visible large cortex) encodes memory by strengthening synaptic connections among vast arrays of neurons that perform higher cognitive functions. *Source*: Fuster, 2004.

CHAPTER

9

Learning and memory

OUTLINE

1.0 INTRODUCTION

Memory can be defined as a lasting representation that is reflected in thought, experience, or behavior. Learning is the acquisition of such representations, which involve a wide range of brain areas and activities. Human memory has some surprising limits and some very impressive capacities. For example, most students would like

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

to have a 'better memory' – by which we mean a capacity deliberately to store and recall information, at will, easily and accurately. However, the human brain has not evolved for academic study and testing, which is a very recent cultural invention. Rather, it has evolved for the tasks of survival. Our best memory performance is not for the exact symbol sequences that conventional computers handle so well. Rather, our brains are exceptionally good at dealing with complex, ill-defined, and novel challenges, the kinds that people have to deal with in the real world.

Humans are exceptionally *flexible* in adapting to new conditions. Learning and memory provide the royal road to that flexibility. Our great capacity for learning allows us to use a brain adapted to a neolithic environment and apply it with great success in a world of computers, brain science, and academic learning. There must be something special about our great ability to learn.

Memory storage is believed to involve very widespread synaptic alterations in many parts of cortex. This process is often taken to involve large-scale Hebbian learning, following the rule that 'neurons that fire together, wire together' (see Chapter 3 and the Appendix). Thus, correlated activity between neurons leads to strengthened connections between them, both excitatory and inhibitory. Temporary cell assemblies are thought to maintain immediate memories, while long-term memories require more lasting strengthening of synaptic connections, both excitatory and inhibitory ones. While evidence has been found for these phenomena, we cannot yet observe changed long-term connectivity directly throughout the brain regions where it is thought to occur. Thus, the Hebbian memory trace itself remains an inferential concept.

In some views, all of the cortex may be able to learn by changing synaptic connectivities, from the posterior perceptual regions to the frontal executive and motor cortex (Fuster, 2004). Others focus more on the temporal lobe, which traditional neurology associates with memory functions. The most important brain structures we look at in this chapter are the *neocortex* – the visible outer brain – and the *medial temporal lobes* (MTL), which contain the two hippocampi and their surrounding tissues, Figures 9.1 and 9.2). The MTL is spatially complex, and you should devote some time to the drawing exercises at the end of this chapter to get an overall sense of its shape and location.

Until recently, the hippocampus was believed to be mainly responsible for transferring experiences into memory, but better methods now implicate the entire hippocampal neighborhood, the medial temporal lobes. The MTL overlap with the ancient mammalian smell cortex, which has fewer than the six layers. The

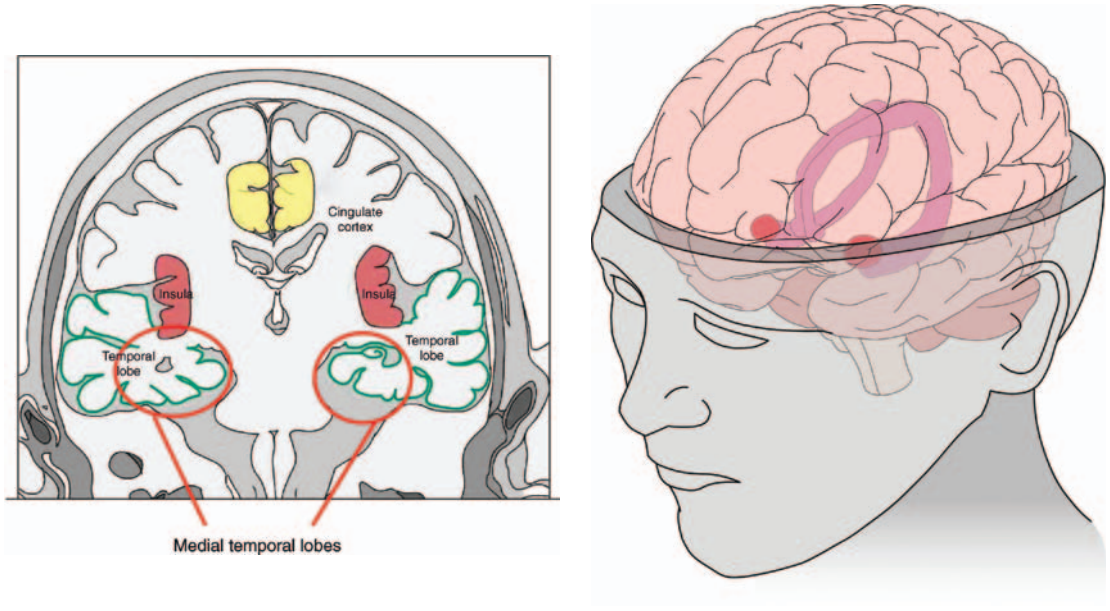


FIGURE 9.1 The medial temporal lobes and hippocampi. The memory regions are spatially complex and difficult to visualize. This collage shows two perspectives. The left panel shows a coronal cross-section of the brain, with the medial temporal lobes (MTL) circled in red. The right panel shows the hippocampi in both hemispheres, tipped by red structures, the amygdalae. Notice that the hippocampi are looped structures, nestled inside of each temporal lobe. The MTL includes the hippocampi and neighboring 'rhinal' structures (see Chapter 5). *Source*: Drawn by Shawn Fu.

neocortex, which is the 'new' cortex of modern mammals, consistently has six layers, one of its most distinctive features. The giant neocortex and the MTL are in constant dialogue with each other, as we store and retrieve the flow of our daily experiences.

Because of its ancient evolutionary lineage, the MTL has multiple functions. The hippocampus was first studied as a map for spatial localization in rats and other mammals. However, it also encodes olfaction, which is why parts of the MTL are called the 'rhinal', 'entorhinal', and 'perirhinal' cortex. ('Rhinos' means 'nose' in Greek, as in the word rhinoceros, 'nose horn').

MTL also interacts with visual area IT, the inferior temporal lobe (see Figure 9.2). You may remember that area IT has been shown to integrate high-level visual object information (see Chapter 6). Neurons firing in this region correlate with conscious visual perception (Sheinberg and Logothetis, 1997). Thus, the MTL is strategically located to take in high-level, presumably conscious visual information.

Just around the corner from the MTL is the auditory cortex, suggesting that auditory information can be fed to MTL as well (see Chapter 7), and the amygdalae reside near the tip of the hippocampi, a major hub of emotional information. Thus, MTL is a highly interactive crossroads, well-placed for integrating multiple brain inputs, and for coordinating learning and retrieval in many parts of the neocortex. It is a 'hub of hubs' (Figure 9.3).

Most of human cortex is neocortex, which ballooned out from earlier regions over more than a hundred million years of mammalian evolution. As mentioned above, the neocortex is believed to encode long-term memories by altering synaptic connections between billions of neurons. There are literally trillions of such synapses in the cortex and its satellite organs, especially the thalamus (see Chapter 3). The hippocampus is ideally situated to combine information about the cognitive (neocortex) and emotional (limbic) areas, and bind that information into a memory trace that codes for all aspects of a consciously experienced event (Moscovitch, 1995).

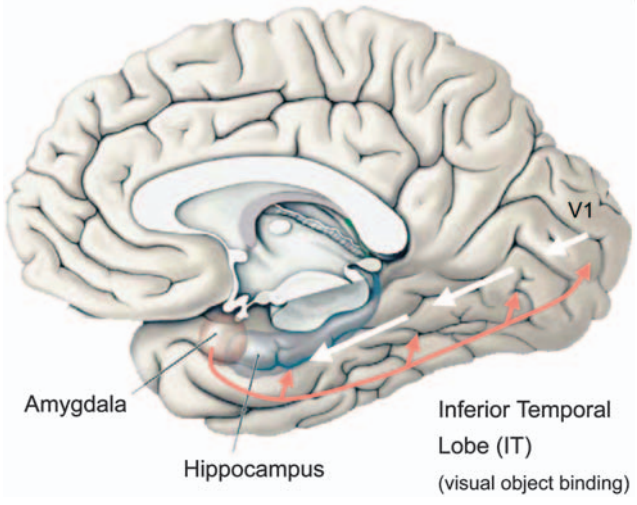


FIGURE 9.2 Memory areas receive visual object information. This midline view shows that the medial temporal lobe (MTL) is closely connected to area IT, the inferotemporal cortex. Area IT seems to support conscious visual object perception (see Chapter 8). MTL also includes the amygdala. Auditory cortex is located just around the corner, on the outside of the temporal lobe. *Source*: Vuilleumier, 2005.

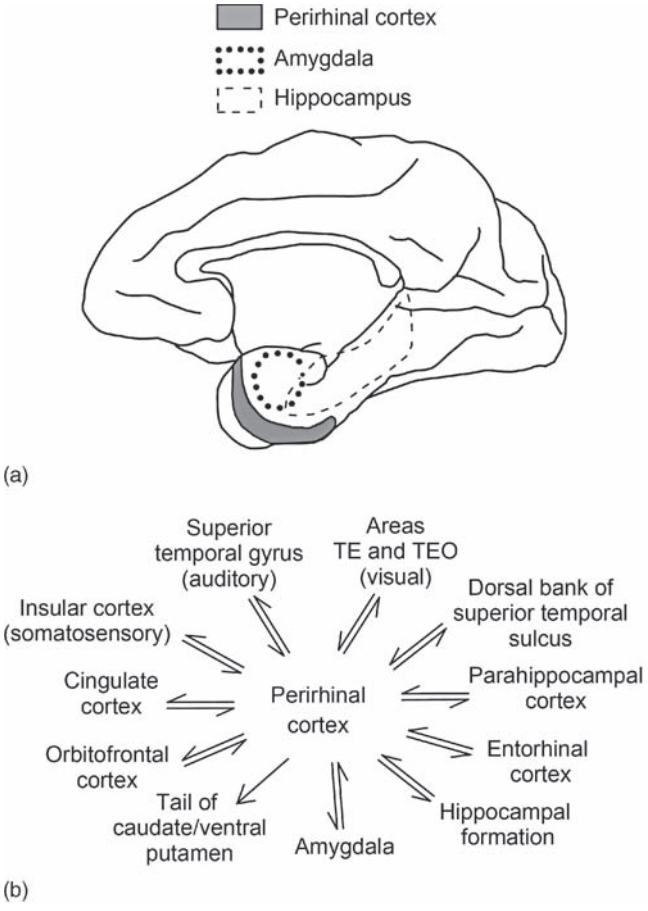


FIGURE 9.3 The medial temporal lobe is a hub with widespread connections. The MTL, including the perirhinal cortex, has very wide connectivity to visual, auditory, somatosensory, emotional, motor, memory, and executive regions. This makes the MTL an ideal place to receive, bind, and distribute information for long-term memory. Notice that almost all connections run in both directions (double arrows). *Source*: Murray and Richmond, 2001.

1.1 A functional overview

Figure 9.4 suggests that the visual cortex (for example) first takes in the sight of a coffee cup on a table. Cortical activity corresponding to the perceived coffee cup then spreads to the MTL, which activates and 'binds' widespread memory traces in both the visual cortex and other regions. Some scientists believe that, for a brief period of time, a few tenths of a second, the visual input regions and other parts of the 'bound' neocortex resonate with each other, as shown in coordinated gamma electrical activity (often called the '40 Hertz hypothesis') (Llinas and Pare, 1991; Engel and Singer, 2001; Freeman *et al.*, 2003). Comprehending a visual stimulus like a coffee cup probably requires several hundred milliseconds. Thus, in less than a second, visual cortex has identified an object in front of our eyes, and triggered MTL to bind many regions of the neocortex to start making memory traces. However, as we will see, a permanent memory takes more time to consolidate.

Memory is for use in the real world, and retrieval is therefore as important as learning. When we encounter a reminder of a specific past experience of the coffee cup, the bound memory traces 'light up' the corresponding regions of cortex again. We thereby *reconstruct* some part of the original memory, again using the MTL to integrate memory traces into a coherent conscious experience. That experience – of imagining yesterday's coffee cup – makes use of visual cortex again. Because this is the central theme of this chapter, we begin with a cartoon version in Figure 9.4.

Learning is not limited to the neocortex. Other types of learning use other parts of the brain (see Section 8.0). However, in this chapter we will focus on learning and retrieving everyday memories.

1.2 Learning and memory in the functional framework

According to our functional framework, sensory input goes to 'working storage', which is part of *working memory* which, in turn, allows information to be actively maintained and manipulated (Figure 9.5; see Chapter 2). Working memory allows us temporarily to retain small

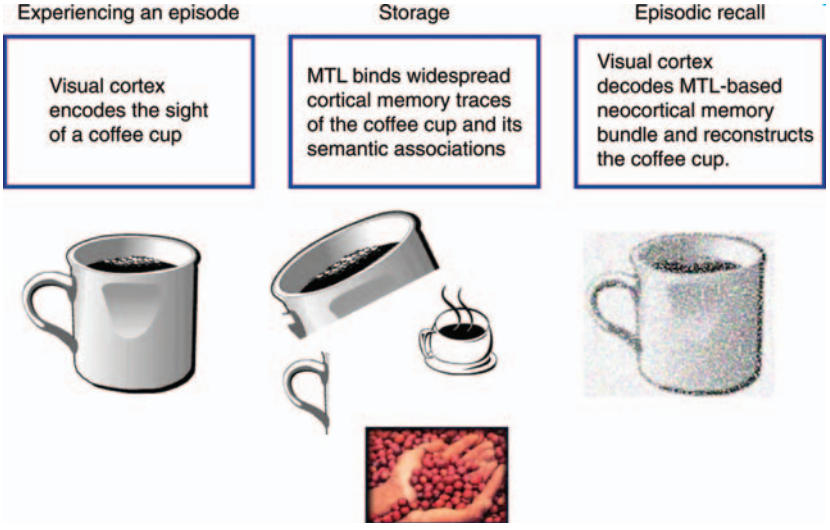


FIGURE 9.4 How MTL is believed to help store and retrieve episodic memories. In the left panel, the sight of a coffee cup standing on a table activates visual cortex up to the level of object perception (see Chapter 6). In the middle panel, storage is achieved when MTL coordinates widespread memory traces (involving synaptic modification) throughout many parts of cortex. These include semantic associates of the coffee cup, such as the coffee beans in the picture below. Visual features of the cup, like the handle, are also part of the associative complex that becomes activated. When the *episodic memory* – the sight of the coffee cup – is cued the following day, maybe by someone asking, 'Did you like the way I made the coffee yesterday?', MTL is once again involved in retrieving and organizing widespread cortical memory traces. Visual cortex is therefore needed to reconstruct the sight of the coffee cup, which is never identical to the original cup, but rather a plausible recreation of a pattern of visual activation that overlaps with the first one. Notice that visual cortex is involved in perception, learning, and episodic recall.

amounts of information in an accessible form. Many everyday tasks call upon this working memory capacity, such as keeping a phone number in mind for the several seconds it takes to dial the number. Working memory also gives us a sense of continuity over time, by embedding our immediate conscious experiences into a longer psychological present. There is debate about the exact relationships between conscious events, working memory, and selective attention. Some scientists believe that working memory (WM) gives rise to our conscious experiences; others suggest that working memory is itself coordinated by conscious cognition (Baars and Franklin, 2003). But there is good agreement that all three interact very closely. That is the most important point.

Two key properties of WM are its relatively small capacity and its limited duration. In his famous paper on the *span* of immediate memory, George Miller (1956) concluded that only seven (plus or minus two) items can be held in immediate memory at any one time. More recent work suggests that the true WM span may be even smaller, closer to four items when rehearsal is prevented (Cowan, 2001; see Chapter 2). Likewise, the time an item is available is quite short, on the order of seconds.

Why have we evolved a memory system with these limits? The answer is not known. One possibility is that WM limits give special status to only the few pieces of information that are most relevant to our present goals, thus protecting them from interference from irrelevant information. It might also be adaptive for items in working memory to fade quickly. If material lingered beyond its period of relevance it might block out new information.

How we interpret and deal with material in working memory is determined by our current goals and concerns, as well as by our existing knowledge. Sensory and internal information may be brought to consciousness using attention. Once it becomes conscious, a number of theorists maintain that information is rapidly *encoded* into long-term memory (e.g. Moscovitch, 1990). There is also evidence for some unconscious

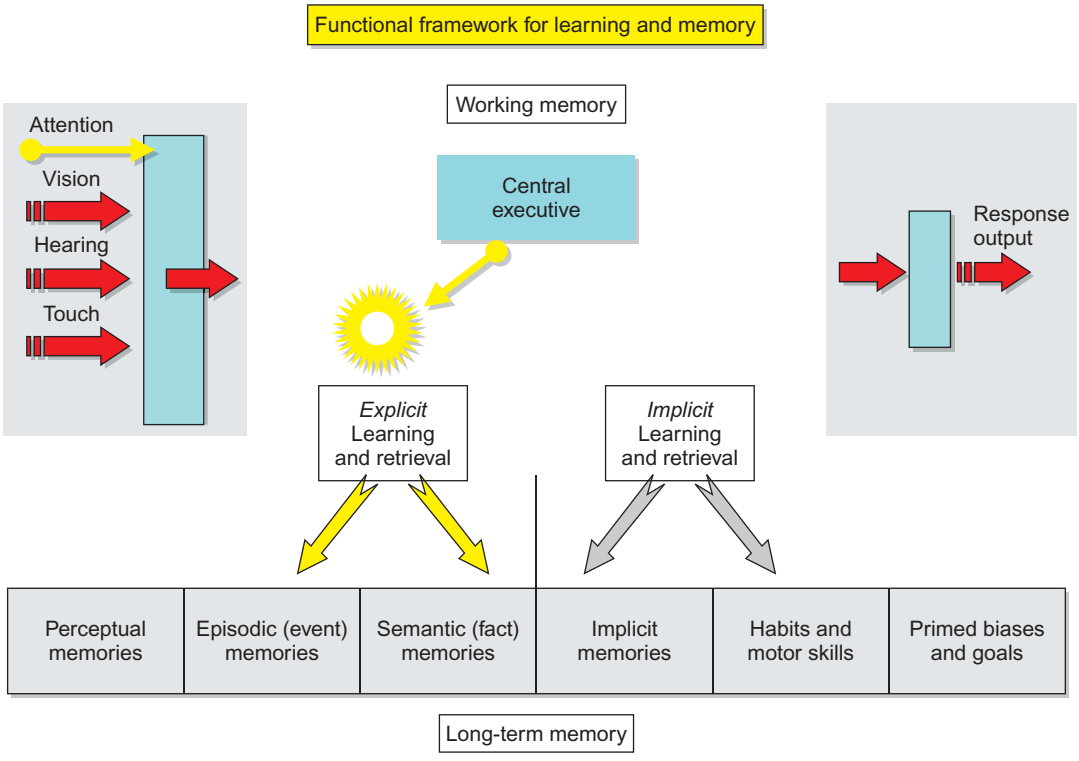


FIGURE 9.5 Explicit and implicit aspects of memory. A functional diagram for learning and memory. Working memory (on top) can now be viewed as input to different types of long-term memory, divided into *explicit* and *implicit* ones. Explicit learning and retrieval involve conscious knowledge, both for facts and autobiographical experiences. Memory for facts is called *semantic* memory, while autobiographical memory is also called *episodic* because it reflects life episodes. Working memory can manipulate explicit memories, like words, numbers, semantic facts, and autobiographical episodes. Implicit learning and retrieval involve primed tasks, highly practiced habits, and motor skills.

learning, but so far only unconscious fear conditioning has been shown to result in long-term memory (LeDoux, 1996). In general, conscious exposure correlates well with learning. While details of this broad picture continue to be debated, it is a useful outline to start with.

Figure 9.5 brings out several features of learning and memory. Notice that conscious cognition leads to *explicit* learning and memory retrieval in this figure. An obvious example is deliberately trying to memorize a technical term in cognitive neuroscience. What may not be so obvious, however, is that *implicit* learning also happens along with learning of conscious or explicit stimuli (Section 2.4).

Thus, Figure 9.5 shows both explicit or conscious *and* implicit or unconscious learning. Episodic memory is the storage of conscious episodes (also called autobiographical memory). Semantic memory, usually viewed as memory for facts, is also conscious, in the strict sense that people can accurately report the facts they believe. This is the standard operational definition of conscious brain events (see Chapter 8). Finally, perceptual memory capacities, such as our ability to 'learn to hear' music and art, also involve conscious, explicit kinds of memories.

On the right-hand side of Figure 9.5 we also see the learning of implicit memories. Infants may hear sequences of speech sounds, but they are not explicitly learning the rules and regularities of grammar. Those are apparently learned unconsciously, as we will see later. In general, implicit learning is often evoked by explicit, conscious events, but it often goes far beyond the events given in conscious experience (Banaji and Greenwald, 1995). Over-practiced habits and motor skills are also largely implicit. As we will see, priming effects are often implicit. Contextual phenomena are often implicit, such as the assumptions we make about visual space, the direction of the incoming light in a visual scene, the conceptual assumptions of a conversation, and so on. These are often hard to articulate, implicit, and to some degree unconscious (Baars, 1988).

As we will see, the 'central executive' of working memory plays an important role in long-term learning and retrieval. For example, if you are trying to learn a word, you might deliberately rehearse it to yourself, using your executive capacities to control inner rehearsal and to shut out distractions. When you are studying for a test, it is a good idea to monitor your own performance 'metacognitively' – i.e. to think about your own thinking process, and to see if your understanding of the material is good enough to pass the exam. All these are examples of executive processes (see Chapters 10, 11, and 12).

1.3 Implicit and explicit memory

Implicit memory is not accompanied by conscious awareness that one has a memory; the memory's existence is inferred only from the effects it has on behavior. Implicit memories may be retrieved without an intention to remember. Priming effects are used extensively to test for implicit memory.

Priming refers to the effect of a stimulus in creating readiness for a similar one. For example, showing a picture of a face will increase the processing efficiency of a following face, as measured by faster reaction time and greater accuracy. Priming can be either perceptual or conceptual.

Suppose you are asked to read a set of words and then your memory for them is tested a week later. We could test your memory directly by asking you to recall as many of the studied words as you can remember, or to recognize the words by picking them out from a list of old and new words. If the interval is long enough, you are likely to recall or recognize only a small subset of the items, and mistakenly classify old words that you studied as new ones that did not appear on the list.

However, if your memory is tested indirectly by asking you to read the words as quickly as you can, you will be able to say old words faster than new words. The old words are *primed*. On such an indirect test no mention is made of memory, and the subject is typically not even aware that memory is being tested. Yet by looking at how quickly subjects read a word we can tell whether the previous experience left a residue in memory. The same result can be seen in amnesic patients who cannot recall studying the words at all.

In the case of conceptual or semantic priming, words such as 'food' may increase the processing efficiency of words like 'water', even though they share little perceptual content. Priming can be viewed as a way of tapping into the general tendency of the brain to engage in predictive processing at every moment.

Perceptual priming is based on alterations of perceptual representation in posterior neocortex associated with perceptual processing. Conceptual priming is associated with alterations of conceptual systems in prefrontal cortex.

1.3.1 Procedural memory

Procedural memory refers to sensorimotor habits or automatic skills, which are largely unconscious. The structures implicated in these habits are the basal ganglia.

> Imagine you are riding a bicycle, and you start falling to the right. How would you avoid the impending

> crash? Many cyclists say they would compensate by leaning towards the left, but that action would precipitate the fall. When responding to the same situation while actually riding a bicycle, these same cyclists would turn their handlebars in the direction of the fall. The example highlights the distinction between implicit and explicit knowledge. Implicit learning refers to the ability to learn complex information (e.g. skills such as bicycle riding) in the absence of explicit awareness. Anecdotes such as the bicycle example offer subjectively compelling demonstrations for the existence of implicit forms of knowledge that are distinct from (and possibly in conflict with) explicit knowledge . . . (Curran, 2001).

The basal ganglia-frontal networks are the mediators of different classes of sensorimotor learning (Yin and Knowlton, 2006).

2.0 AMNESIA

Chapter 2 touched on the case of Clive Wearing, who has lived with a dense amnesia since 1985, when a viral infection destroyed some brain areas for memory. Over a few days, Wearing was transformed from a rising young musician to a man for whom each waking moment feels like the first, with almost no recollection of the past, and no ability to learn for the future.

Little has changed for Wearing since 1985. While he cannot recall a single specific event, some aspects of his memory are spared. He can carry on a normal, intelligent conversation. Some short-term memory is spared, allowing him to stay with a topic over several seconds. His has retained general world knowledge, an extensive vocabulary, and a tacit understanding of social conventions. Wearing also remains a skilled musician, able to play complex piano pieces from sheet music. Though he cannot remember specific events, he does recall a limited number of general facts about his life. Among the few memories that have survived is the identity of his wife, Deborah. He greets her joyfully every time she comes into his room, as though they have not met for years.

However, just moments after she leaves, Wearing has forgotten that she was there at all. In a recent book, Deborah Wearing (2005) tells of coming home after visiting Clive at his care facility, and finding these messages on her answering machine:

> Hello, love, 'tis me, Clive. It's five minutes past four, and I don't know what's going on here. I'm awake for the first time and I haven't spoken to anyone. . . .
>
> Darling? Hello, it's me, Clive. It's a quarter past four and I'm awake now for the first time. It all just happened a minute ago, and I want to see you. . . .
>
> Darling? It's me, Clive, and it's 18 minutes past four and I'm awake. My eyes have just come on about a minute ago. I haven't spoken to anyone yet, I just want to speak to you.

Wearing's history suggests that amnesia is selective – certain kinds of memory may survive while others are lost. Skills like the ability to speak or play the piano are distinct from our memories of specific events. Thus, *memory is not unitary, but consists of different types*. Wearing's history also hints that different parts of the brain may be involved in different kinds of memory.

Figure 9.6 shows how specific Clive Wearing's memory loss is. Organic amnesia – the kind that involves damage to both MTLs – interferes with episodic learning and recall. In addition, semantic learning is impaired, but not semantic retrieval. Clive Wearing still understands the world in much the way he understood it in 1985; his previous semantic knowledge is remarkably intact. But he cannot learn new ideas. And he can neither learn nor remember specific events. We will see later why this pattern of impairment makes sense.

Although all amnesic patients have memory loss, it varies in degree. Clive Wearing's amnesia resembles that of other patients, but he is unusual in his recurrent sense that he has just awoken from some unconscious state. He also 'perseverates' more than most amnesics, repeating the same thoughts and actions over and over again, as in the repetitive telephone messages he leaves for his wife. These symptoms may result from additional damage to prefrontal structures that allow us to monitor our own actions.

2.1 HM: the best-studied amnesia patient

We know a great deal about Clive Wearing's life from the extensive publicity about his case. However, another patient, known only as HM, is by far the best-studied victim of amnesia. In the case of HM we know exactly where the lesion occurred (Figures 9.7 and 9.8). This makes him very rare. Most brain injuries are very 'messy', can spread wider than the visible lesions, and may change over time. Clive Wearing's viral infection apparently destroyed hippocampal regions on both sides of the brain, but also some frontal lobe areas. Wearing may also have suffered brain damage that we simply do not know about. In the case of HM, however, because his lesion was carefully performed by a

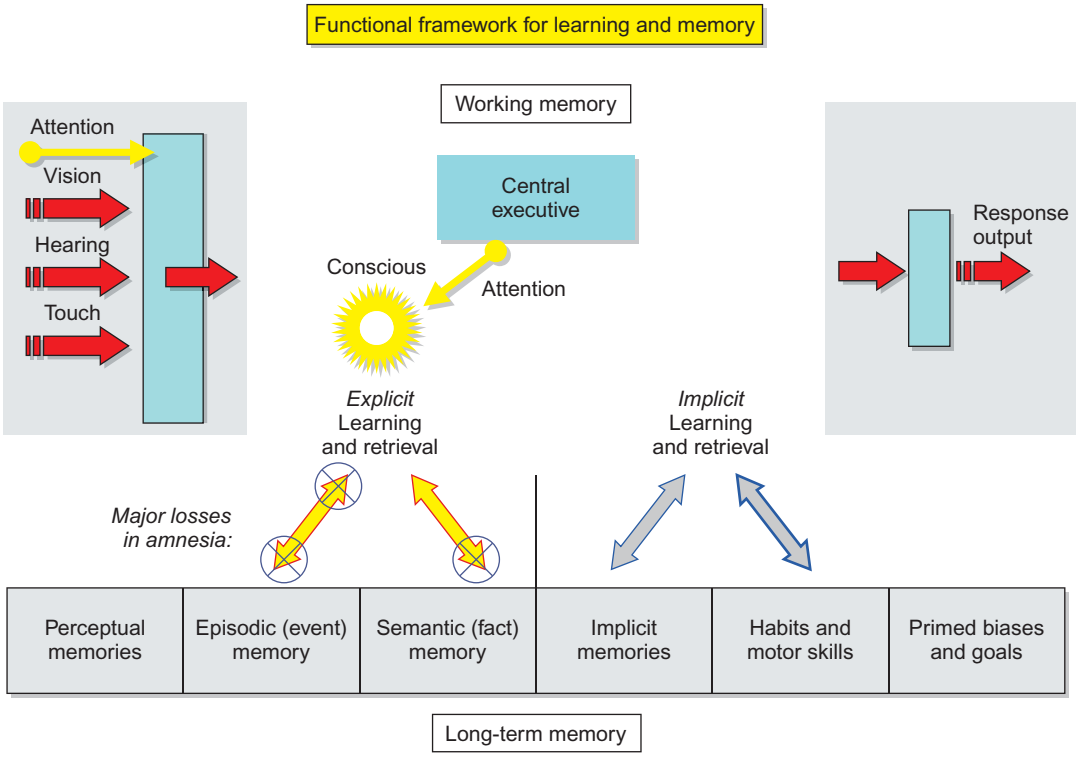


FIGURE 9.6 Functional framework: the typical loss in organic amnesia. Amnesia due to bilateral damage to MTL is highly specific. It impairs recollection of episodic (autobiographical) memories and blocks episodic learning. It also makes it impossible to learn new facts and concepts (semantic learning). However, amnesics like HM and Clive Wearing can carry on a normal-seeming conversation because they can still *retrieve* semantic information that was learned before the injury. *Implicit* learning and retrieval also continue. Since the MTL and neocortex work together to enable episodic learning, damage to MTL on both sides of the brain seems to explain these specific deficits. (Notice that the terms 'explicit' and 'conscious' are essentially equivalent; both are indexed by accurate report, as discussed in Chapter 8. Similarly, 'implicit' and 'unconscious' are equivalent for our purposes).

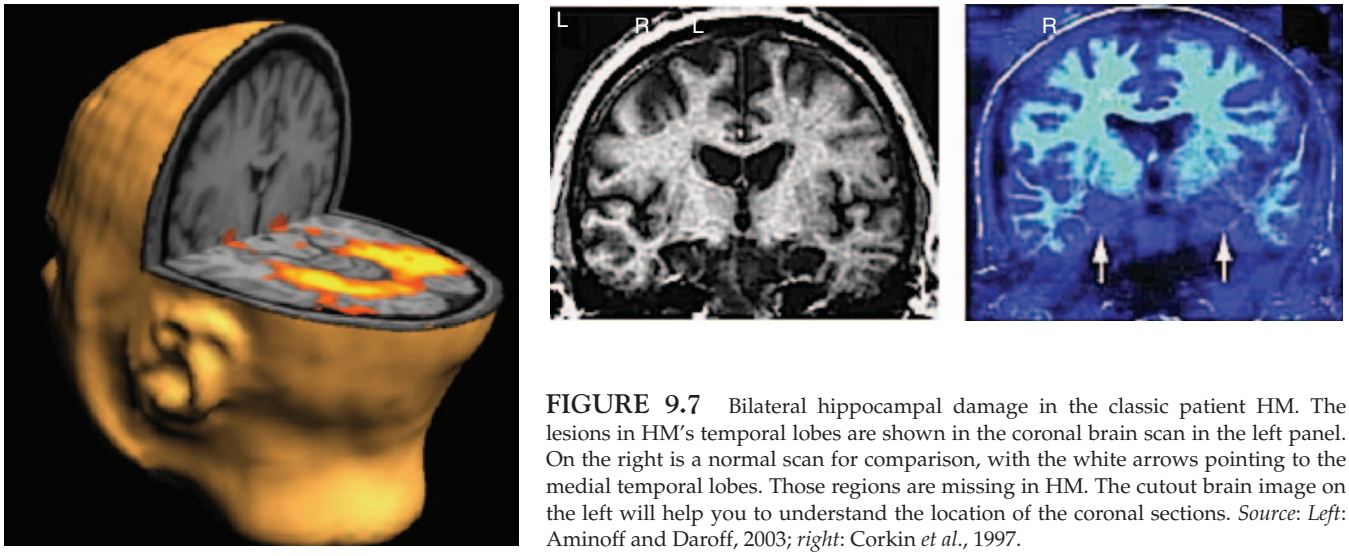


FIGURE 9.7 Bilateral hippocampal damage in the classic patient HM. The lesions in HM's temporal lobes are shown in the coronal brain scan in the left panel. On the right is a normal scan for comparison, with the white arrows pointing to the medial temporal lobes. Those regions are missing in HM. The cutout brain image on the left will help you to understand the location of the coronal sections. *Source*: *Left*: Aminoff and Daroff, 2003; *right*: Corkin *et al.*, 1997.

surgeon, we know that both sides of the medial temporal lobe (MTL) were removed as accurately as was possible at the time. The extent of HM's brain damage and functional deficits have been verified with great care, in more than 100 published articles. This has made HM one of the most important patients in the history of brain science (Box 9.1).

2.2 A summary of amnesia

HM represents the features of amnesia in a very 'pure' form. More generally, amnesia is any loss of memory for personal experiences and other information, despite otherwise normal cognitive functions. The cause can be organic, including infection,

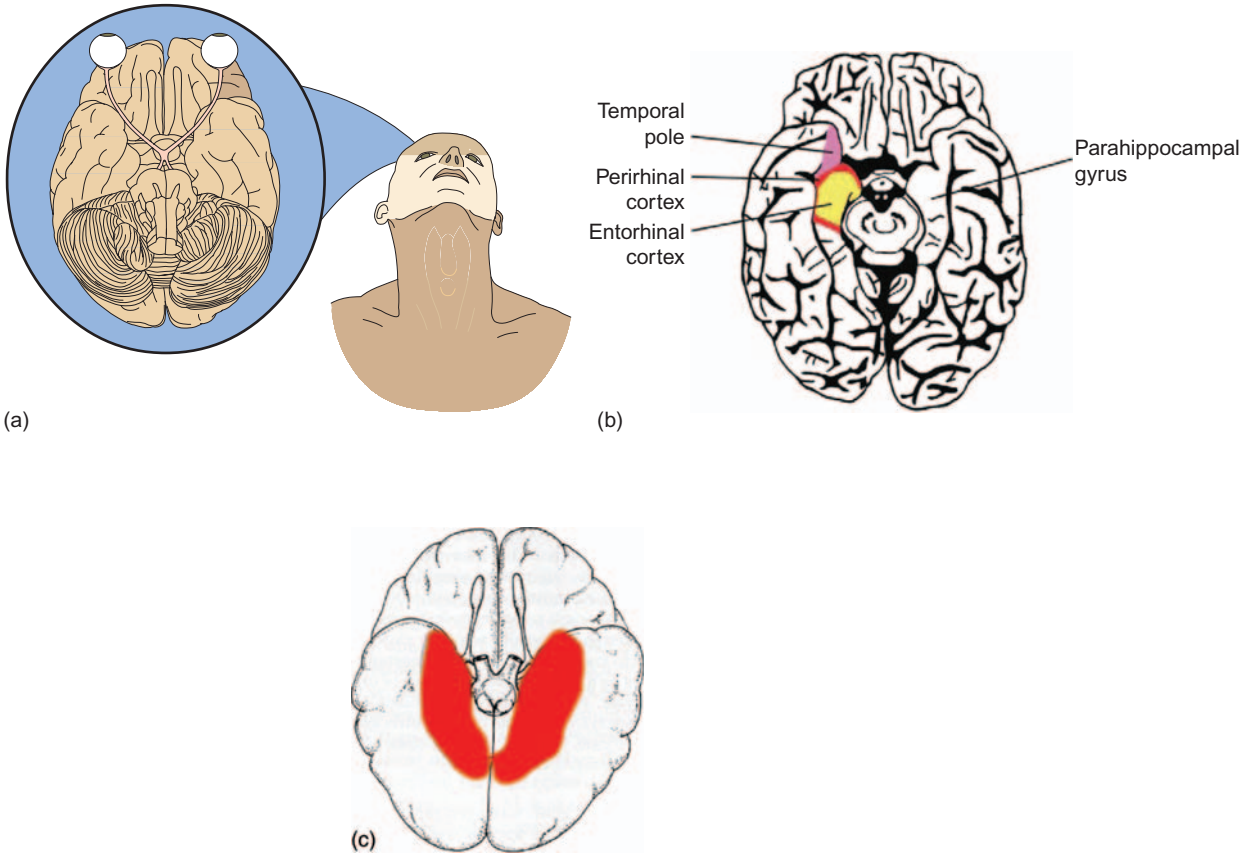


FIGURE 9.8 The medial temporal lobes and HM's lesions, seen from below. (a) The orientation of the head and brain; (b) the bottom of the MTL, with major subregions for memory labeled. Notice that the rhinal (smell) cortices indicate the ancient origin of this region. In all figures you can see the two olfactory bulbs pointing upward, an important landmark for orientation. (c) The surgical lesion in HM's brain. The surgeon at the time was unaware of the importance of this region for memory. *Source*: (b) Buckley and Gaffan, 2006; (c) Morris Moscovitch, personal communication.

BOX 9.1 The case of HM

The cognitive neuroscience of memory arguably began with Herbert Scoville and Brenda Milner's (1957) report of a memory disorder in HM after bilateral removal of his medial temporal lobes to control severe epileptic seizures. As a result of a head injury from a bicycle collision when he was a young boy, HM was beset with epileptic fits that increased in frequency and severity into his late 20s. As a treatment of last resort, Scoville performed an operation in which he removed tissue in and around the hippocampus on both sides of HM's brain (see Figure 9.8). While the surgery reduced HM's seizures, it had a profound and unexpected impact on his memory. This result was unknown at the time, and Scoville would undoubtedly have changed the procedure had he known about this harmful result. The report of HM's case by Scoville and Brenda Milner (1957) was the first to demonstrate directly the importance of the hippocampus and surrounding structures for memory.

As a result of the operation, HM could not remember any of the events of his life thereafter – the people he met, the things he did, events taking place in the world around him. As an adult, he could not keep track of his age, and could no longer recognize himself in the mirror because he was unfamiliar with his changed appearance.

(*Continued*)

BOX 9.1 (Continued)

In addition to this *anterograde* (post-damage) memory deficit, HM also could not remember events or experiences from the years immediately before the surgery, a *retrograde* amnesia. While his episodic (autobiographical) memory loss was acute, other cognitive functions seemed to be intact. He could reason, solve problems, and carry on a normal conversation. His intelligence was normal, and he retained his language abilities.

HM had intact short-term memory. He performed like healthy controls on tests of working memory, such as the digit span task. HM had been under the care of doctors from a young age, and his intellectual abilities before surgery were well documented. The specific locus of damaged tissue was both limited and well characterized. In most amnesias, the damage is more widespread and difficult to identify. HM had been tested and imaged a number of times since his surgery, giving a very complete picture of his condition.

As you can tell from Figures 9.1 and 9.2, HM had an apparently intact neocortex – the outer structures in brain scan. Like Clive Wearing, HM could carry on a normal conversation. He could discuss the immediate present, using his general knowledge of the world. He was conscious, had normal voluntary control over his actions, and appeared to be emotionally well adjusted. It was only when his episodic memory was tested that he revealed that he simply could not remember the past, or learn new memories for the future.

It is useful for you to review some important regions of the cortex (Figures 9.3, 9.9;). You should recall the location of the prefrontal lobes particularly, in front of the motor and premotor cortex. All of the neocortex is important for memory but the prefrontal lobes may be especially important.

stroke, tumor, drugs, oxygen deprivation, epilepsy, and degenerative diseases, such as Alzheimer's disease. Amnesia can also be *psychogenic*, resulting from trauma or suggestion (Nilsson and Markowitsch, 1999).

As we have seen, organic amnesia is caused by bilateral damage to the medial temporal lobes, which includes the hippocampal formation. It generally reveals:

1. *Impaired memory but preserved perception, cognition, intelligence, and action*. Amnesic people perform normally on standard tests of intelligence, but are impaired on standard tests of memory. They can play chess, solve crossword and jigsaw puzzles, comprehend complex instructions, and reason logically.
2. *Impaired long-term but not working memory*. Amnesic people have a normal digit span. They are impaired, however, if they are distracted. The same holds for words, stories, visual patterns, faces, melodies, smells, and touch.
3. *Impaired recent but not remote memories*. Memory loss is most noticeable for events learned *after* the onset of the disorder, as well as in the period immediately preceding it, but not for information acquired years before. That is, amnesia victims have an *anterograde amnesia* that extends into the future but a limited *retrograde amnesia*. The length and severity of retrograde amnesia varies.
4. *Impaired explicit but not implicit memory*. Anterograde (post-injury) memory loss applies only to information that can be remembered consciously or *explicitly*. Learning, retention, and retrieval of memory without awareness or *implicitly* is normal.

2.3 Spared functions in amnesia: implicit and procedural memory

As mentioned above, implicit memory is commonly assessed by priming tasks. Perceptual priming is mediated by sensory cortex, and conceptual priming is believed to involve both the temporal and prefrontal regions. Amnesics do not lose their capacity to perform well on priming tasks, such as word-fragment completion. For example, subjects may study a list of words (such as *metal*) and are tested with fragments of the words they studied, to see if they can complete them (*met__*). The study phase increases the speed of completion. On such tasks, amnesic patients can perform as well as normals.

Functional neuroimaging studies confirm the perceptual locus of perceptual priming. Unlike tests of explicit memory, which are associated with *increased activation* during retrieval in regions that support memory performance, such as the MTL and prefrontal cortex, perceptual priming is associated with *decreased activation* on repeated presentations in regions believed to mediate perceptual representations. Thus, repeated presentation of faces and words leads to decreases in activation in inferior temporal and extrastriate cortex which mediate face and word perception (Wigg and Martin, 1998; Schacter *et al*., 2004).

2.3.1 Conceptual priming

In conceptual priming the relationship between study and test items is meaning-based. Conceptual tasks

include word association ('Tell me the first word that comes to mind for Elephant'), category exemplar generation ('Provide examples of animals'), and general knowledge ('What animal is used to carry heavy loads in India?') (Moscovitch *et al*., 1993; Roediger and McDermott, 1993). Conceptual priming occurs if studied words (e.g. elephant) are retrieved more frequently than unstudied ones. Because conceptual priming depends on meaning, a change in the physical form of stimuli has little influence on conceptual priming.

Conceptual priming is impaired in people with damage to regions of cortex mediating semantics. Thus, patients with semantic dementia whose degeneration affects lateral and anterior temporal lobes show an inability to recognize repeated objects which share a common meaning, for example, two different-looking telephones. But they have no difficulty recognizing the object if it is repeated in identical form (Graham *et al*., 2000).

Likewise, patients with Alzheimer's disease show preserved perceptual priming but impaired conceptual priming. Functional neuroimaging studies of conceptual priming implicate semantic processing regions, such as prefrontal and lateral temporal areas. As in tests of perceptual priming, tests of conceptual priming lead to decreases in activation in those regions (Buckner *et al*., 1998; Schacter *et al*., 2004). Asking people repeatedly to generate examples of 'animals' results in *reduced* activation in the same regions.

Numerous studies have shown that priming on a variety of tests is normal in amnesic patients. This applies to most tests of perceptual and conceptual priming, indicating that the MTL does not contribute to them.

2.3.2 Spared procedural memory in amnesia

One of the earliest demonstrations of preserved memory in amnesia was on tests of learning perceptual motor skills called *procedural memory*. Corkin (1965) and Milner (1965) showed that HM was able to learn and retain a pursuit-rotor task, keeping a pointer on a moving target. HM showed improvement on these tasks even months later, though he could not recall doing it even minutes afterward if he was distracted. These findings have been repeated in other cases.

Procedural memory depends on perceptual-motor regions, like the basal ganglia, which interact with the neocortex, both the posterior and frontal (see Chapter 5). Patients with impaired basal ganglia due to Parkinson's or Huntington's disease show little or no improvement after practicing sensorimotor tasks (Kaszniak, 1990; Gabrieli *et al*., 1994).

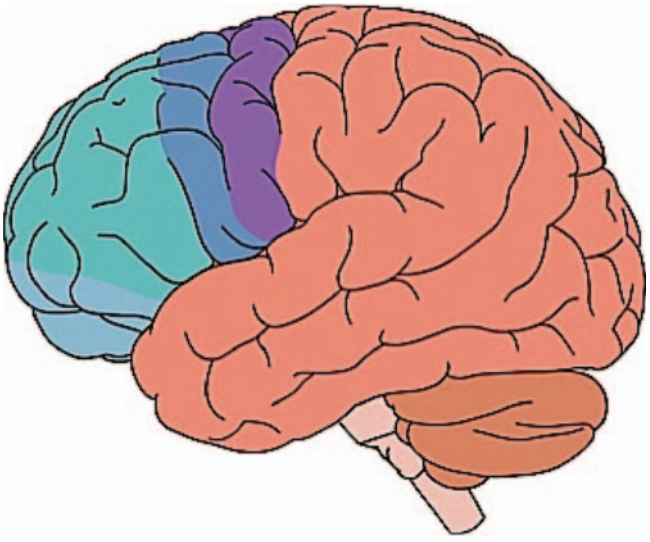


FIGURE 9.9 Neocortex: motor, premotor, and prefrontal regions. In this lateral view of the cortex, the motor strip is tinted purple, and just in front of it, the premotor area encodes the cognitive intention to move specific limbs. The true prefrontal cortex is in front of these motor regions (light green). The light blue area of the prefrontal lobe is sometimes called the orbitofrontal cortex, because it is located just above the orbital hollows of the two eyes. You are encouraged to review the other visible structures, including the major lobes, the Sylvian fissure, and the central sulcus, which divides the posterior half of cortex from the frontal half. *Source*: Drawn by Shawn Fu.

In the serial reaction time task (SRT), dots are presented on a computer screen in one of four locations, and participants are instructed to press a key corresponding to the location of the dots they see (Willingham *et al*., 1989). Some of the sequences are repeated while others change randomly. Reaction time to the repeated sequences becomes faster with repetition, but remain the same for the random sequences, even though participants cannot consciously distinguish one from the other (Willingham, 1998). Amnesic patients perform normally on the implicit SRT task but poorly on the explicit version (Nissen and Bullemer, 1987; Reber and Squire, 1998). Again, patients with basal ganglia disorders like Parkinson's disease perform poorly on both SRT tasks (Knopman and Nissen, 1987; Vakil *et al*., 2000).

Functional neuroimaging studies also show that learning on the implicit SRT task is associated with activity in the basal ganglia but not with MTL activity.

2.4 Spared implicit learning

Academic learning is often explicit: professors point out the things to be learned, and students try their best to memorize them. But most ordinary human learning is probably implicit. A hunter may teach young people how to track an animal or how to kill and skin it. Most of the time such practical activities can be taught more easily by modeling than by explicit labeling. Many of the subtleties of hunting and gathering may not even have names. Experimentally, subjects who are given a set of stimuli generated by a simple set of rules unconsciously infer the underlying regularities. Social habits are probably learned mostly implicitly. Children learning language surely don't label the words they hear as nouns or verbs. Rather, they pay attention to speech sounds and the underlying regularities are learned *implicitly*. We rarely become conscious of abstract patterns – the regularities of grammar, the harmonic progressions of a symphony, or the delicate brushwork of a work of art. Most knowledge is tacit knowledge; most learning is implicit.

Knowlton *et al*. (1994, 1996) used a probabilistic classification task to study implicit learning. Participants were shown sets of four cards that predicted the 'weather' with different probabilities (Figure 9.10). After each set of cards, participants were asked whether it predicted 'rain' or 'sunshine'. Some sets predicted 'rain' 20 percent of the time, and others 80 percent of the time. Learning this association takes about 50 trials in normal people, but it takes considerably longer for subjects to realize explicitly which card sequence predicted which kind of weather. That is, the weather prediction is learned *implicitly* before it can be stated *explicitly*.

Amnesia patients performed as well as controls in the early trials, the implicit association, but not in the later trials when performance was based on explicit, declarative memory. However, patients with Parkinson's disease, a basal ganglia dysfunction, performed poorly during the early trials, but caught up during the later ones. Brain imaging showed activity in the basal ganglia throughout the task but a shift in MTL activity as the task progressed (Poldrack *et al*., 1998).

In summary, amnesia due to bilateral damage to MTL seems to be primarily a disorder of *episodic*

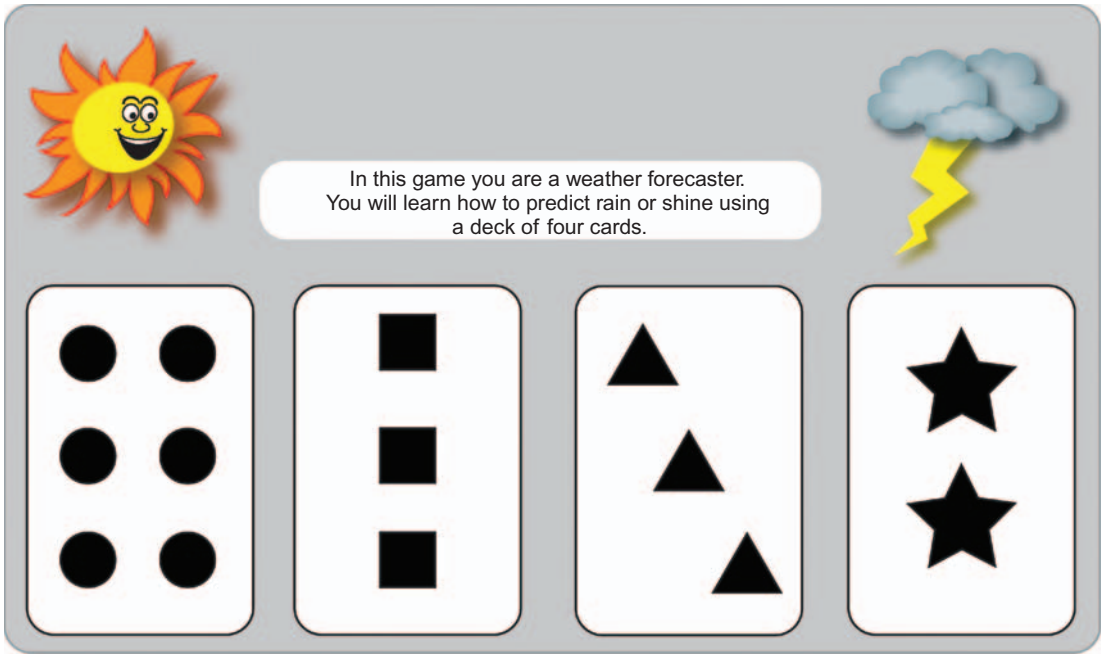


FIGURE 9.10 An implicit 'weather prediction' learning task. Knowlton *et al*. (1994) devised this 'weather prediction' task for four-card sequences. Participants learned to predict the probabilistic outcomes implicitly before they were able to state the pattern explicitly. Amnesic patients performed well during the implicit early part of the learning process, but did not learn to state the association between the cards and the 'weather' explicitly. *Source*: Knowlton *et al*., 2003.

memory, resulting from impaired transfer of information from working memory into long-term memory. Because memories acquired long before the onset of amnesia are relatively spared, it is believed that the hippocampus and related structures in the medial temporal lobe are needed only temporarily to hold information in memory until they are consolidated elsewhere in the brain, presumably in neocortex.

FRONTIERS OF COGNITIVE NEUROSCIENCE

Episodic memory

FIGURE 9.11 Charan Ranganath, PhD, University of California, Davis, CA, USA.

The great psychologist Endel Tulving (Tulving, 1985) described *episodic memory* (the ability to remember a past event) as "mental time travel." It took neuroscientists a couple of decades to catch up with Endel, but we now understand that episodic memory allows us to reexperience the past, stay oriented in the present, and plan for the future (Schacter *et al.*, 2007). Tragically, memory is significantly affected by numerous neurological (e.g. Alzheimer's disease, fronto-temporal dementia, epilepsy, traumatic brain injury, etc.) and psychiatric (e.g. schizophrenia, depression, post-traumatic stress disorder, etc.) conditions, and the consequences can be debilitating. Accordingly, understanding the functional organization of memory processes and their neural substrates is of supreme importance to both scientists and society.

Until recently, much of what we knew about the neural basis of memory came primarily from animal models and comparison with patients with human amnesia. This research yielded a great deal of information about the types of memory that might be supported by particular neural systems, but what was missing was an understanding of how these systems work in the human brain. Fortunately, when I was in graduate school, researchers began to use brain imaging techniques to identify the neural correlates of memory processes. These techniques have allowed us to develop and test models to explain not only imaging data, but also results from studies at the systems and molecular levels in animals and studies on the functional nature of memory processes in humans.

Of course, the $64,000 question is, have we learned anything from all those pretty pictures? I certainly think so. Since Brenda Milner's groundbreaking work on amnesic patient Henry Molaison ("HM"), we've known that the medial temporal lobe (MTL) region is critical for episodic memory. Imaging studies have added to this picture by demonstrating that different areas of the MTL support memory in different ways (see Figure 9.12). For instance, perirhinal cortex activation is linked to recognition of items based on familiarity, whereas activity in the hippocampus and parahippocampal cortex is linked to recollection of relationships between items and the context in which they were encountered (Diana *et al.*, 2007). This pattern of results converges remarkably with studies of focal MTL lesions in rats and monkeys, suggesting parallels in MTL function that are surprisingly conserved across species (Eichenbaum *et al.*, 2007). Imaging studies have also shown that episodic memory is supported by a cortical network that extends far beyond the MTL. For instance, imaging findings have highlighted the fact that the prefrontal (Ranganath and Blumenfeld, 2008) and posterior parietal cortices (Cabeza *et al.*, 2008) are routinely recruited in the service of memory encoding and retrieval, and we are just beginning to understand the roles of these regions (Figure 9.12).

What I've just described only hints at the potential for future developments in this area. Recent breakthroughs in high resolution imaging, coupled with analysis techniques to detect and classify spatial patterns in imaging data, will lead to significant changes and refinements in

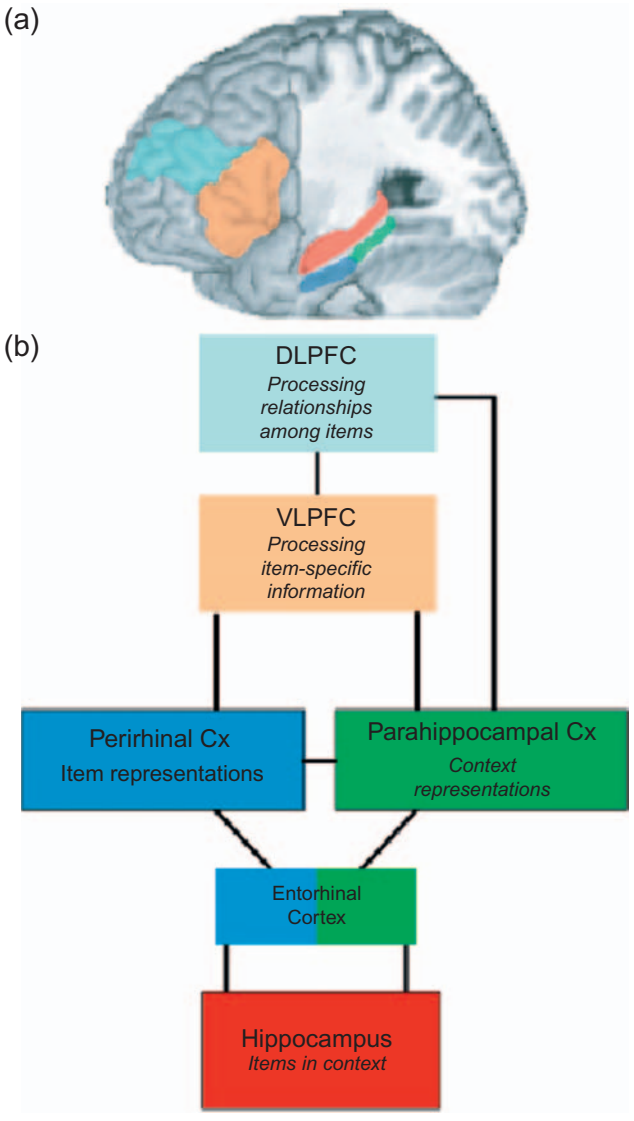


FIGURE 9.12 Prefrontal and medial temporal lobe regions that contribute to episodic memory processing. (a) Relative locations of the dorsolateral prefrontal cortex ('DLPFC'; light blue), ventrolateral prefrontal cortex ('VLPFC'; peach), perirhinal cortex (blue), parahippocampal cortex (green), and hippocampus (red) are shown on a rendering of a brain with a cutaway to reveal the medial temporal lobes. (b) A diagram illustrating our current model of how lateral prefrontal and medial temporal regions may contribute to episodic memory. The anatomical connections between each region are illustrated with black lines and proposed roles of each region are shown in italic text. For simplicity, the diagram presents only the most significant anatomical connections between these regions and omits other anatomically connected regions that also may play a significant role in episodic memory formation or retrieval. *Source*: Ranganath, (in press).

our theories of the neurocognitive processes that support our amazing capability for mental time travel.

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3.0 MEMORIES ARE MADE OF THIS

Traditionally, a memory is considered to be a stable record of an event, which can be recalled accurately in the same form it was learned. In this commonsense view, memories can be retrieved, examined, and played back like a high fidelity music recording. Memories can also be forgotten without affecting other cognitive systems.

There are reasons to question this common sense idea. One is that real memories of past events are rarely accurate. The *process view* considers memory to be a product of a dynamic process, a reconstruction of the past influenced by past and current conditions, anticipations of future outcomes, and other cognitive processes. In the process view, memory is based on stored information, but is not equivalent to it. It is dynamic and mutable, and interacts with other processes. Thus, two people experiencing the same event may have different memories of it. It is not simply that one person is right and the other wrong but that in retrieving the memory each person's outlook, knowledge, motivation, and retentive abilities may alter what is retrieved.

Everyone's memory changes with time. We forget most of what has happened within minutes or hours, and what remains is commonly reorganized and distorted by other knowledge or biases. We would not want computer files or books to be that way. We do not want files to decay over time or to leak into neighboring files. Computers and libraries are designed to keep everything as distinct and stable as possible. Yet normal memories do fade, and are often confused with others.

Try to reconstruct in as much detail as possible all the things you did two weekends ago, in the exact order in which you did them. To do that, most of us have to search for cues to determine exactly what we did. Having found a cue, there is a process of reconstruction, especially in trying to figure out the sequence of events. Did I meet my friend before I spoke to my parents or afterward? Did I go shopping, and what was the order of the stores I visited? In each store, in what order did I look at the merchandise and buy it? You can try this with a recent movie, and then see how accurate your memory is by checking it against a copy of the movie.

To answer these questions you must draw on a body of knowledge and inference that is unlike anything that is needed when you enter a file name to access a computer file or use a call number to find a library book. You may confuse what you did two weekends ago with what happened another time. As we will see, some patients with brain damage have a disorder called *confabulation*, in which they make up false memories without any intention of lying, and without any awareness that their memories are incorrect.

Memories influence how other memories are formed and retrieved. They also shape our actions even when we are not conscious that they do so. Our memories and dispositions influence our thoughts and actions and, in turn, are influenced by them. In short, memory is needed to carry on the affairs of daily life and to plan for the future, and is, in turn influenced by the past, whether conscious or not, and by our thoughts about the future.

3.1 Electrically evoked autobiographical memories

For some 50 years, brain surgeons have reported that awake patients report vivid, specific conscious recollections during temporal lobe stimulation. Penfield and Roberts (1959) were among the first to use pinpoint electrical stimulation of cortex to map out functional regions. Their aim was to remove 'epileptic foci' in the cortex, regions of scarred tissue that can trigger the massive electrical storm of major seizures. In order to locate epileptic foci, and to avoid harming functionally important areas, the cortex of awake patients was mapped using low-voltage electrical stimulation in specific cortical locations.

This is only possible because the cortex itself has no pain receptors. As long as local anesthetic is used to block pain from the scalp incision, conscious patients can talk about their experiences without harm. Open-brain surgery provides a unique source of evidence for cognitive neuroscience.

Stimulation of the temporal lobe sometimes results in an unexpected flood of conscious memories. For example, a recent patient during brain stimulation gave the following reports of his experiences (Moriarty *et al.*, 2001):

1. At four electrode locations shown in Figure 9.13, re-experiencing Flinstones cartoons from childhood
2. At four different electrode locations, hearing the rock band Pink Floyd
3. At two other locations, a baseball announcer
4. At four more locations, an unknown female voice.

Notice that the open circles in the figure show electrode locations that led to no experiential memories at all. Some of the electrode sites are close to the auditory cortex of the upper temporal lobe, but some are not. And these auditory regions are not known to provide such rich memories of experiences that patients report having heard at specific points in their lives. However, this particular patient had a surgical lesion in the medial temporal lobe, and we must be careful about generalization to other cases.

The patient in this case is not told which electrode is currently stimulating the temporal lobe, so that it is not possible to fake this pattern of results. Scientists have been skeptical about these reports, since stimulation in one place might activate other regions as well. Epileptics have atypical brains, since cortex commonly changes in response to disorders. However, it is extremely unlikely that so many different patients would report a flow of conscious memories over fifty years of stimulation of the temporal lobe. After numerous animal experiments, careful studies of amnesic patients and brain imaging of memory tasks, there is little doubt today that there is something about the temporal lobe that is specific to long-term episodic memory. One reasonable hypothesis is that temporal lobe stimulation somehow activates specific memories by way of the MTL.

Figure 9.14 shows a possible explanation of this phenomenon. What we are seeing in the neurosurgical patient is an established memory pattern, which is re-evoked by direct electrical stimulation to the temporal lobe. Thus, the flow of information is from the neocortex (temporal) to the hippocampal system (MTL), which causes the hippocampal system to resonate with the original neocortical memory traces to produce the

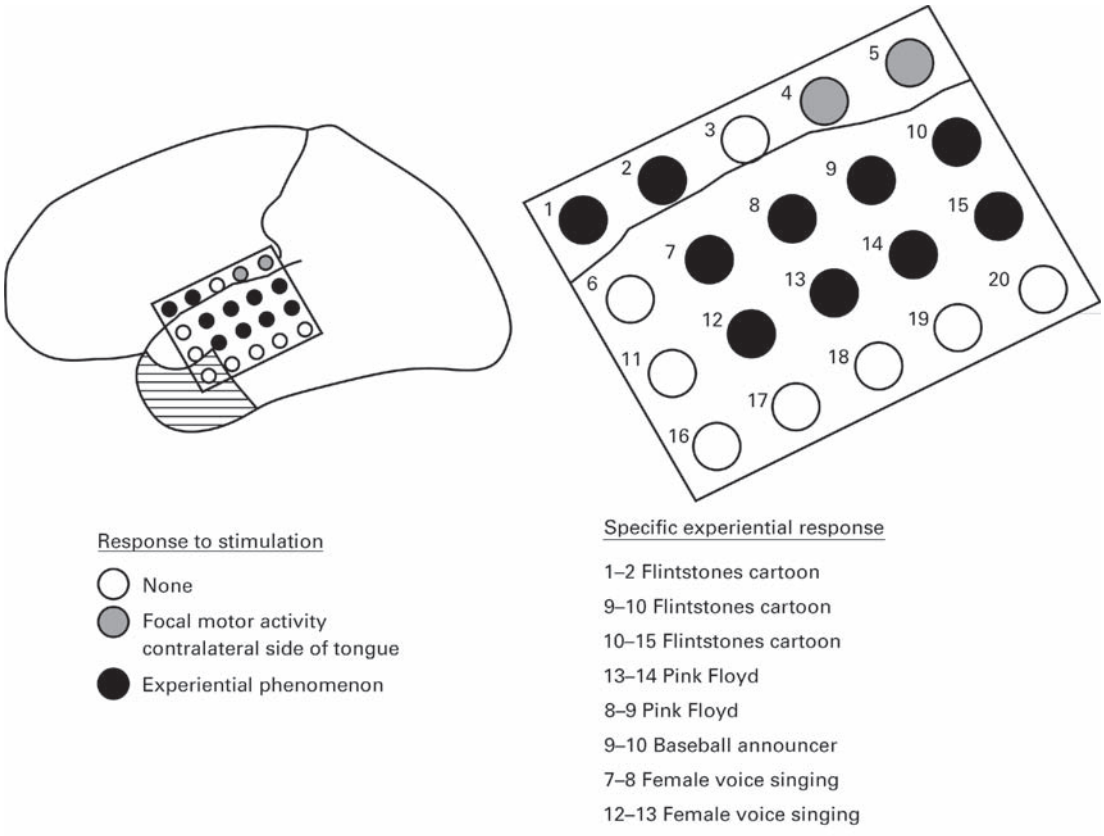


FIGURE 9.13 Autobiographical memories evoked by temporal lobe stimulation. Spontaneous reports of memory experiences by electrical brain stimulation in a patient with a surgical lesion in the left medial temporal lobe. Notice the electrode grid that was placed on the cortex as shown. Electrodes were places 1 cm apart. Different electrodes consistently evoked different memory episodes. Spontaneous reports of this kind are not unusual with temporal lobe stimulation, but are not routinely reported as a result of other locations of cortical stimulation. *Source*: Moriarty *et al*., 2001.

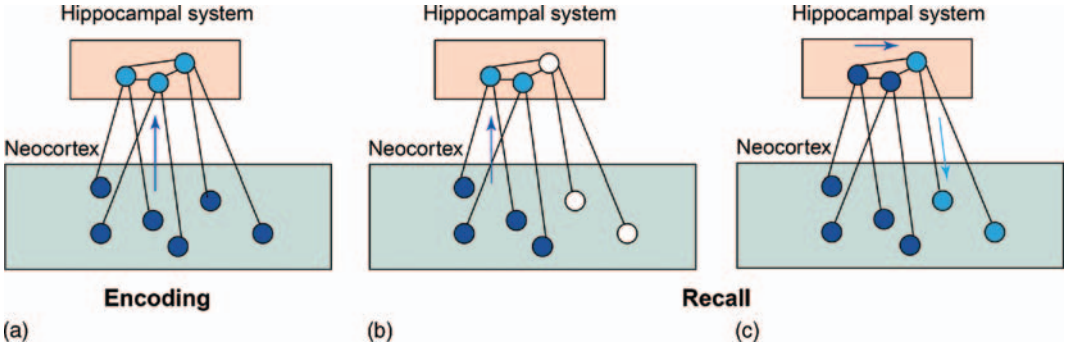


FIGURE 9.14 The hippocampal system (MTL) and neocortex in learning and recall. A neural net model of MTL (the hippocampal system) in interaction with neocortex. During the encoding or learning process (a), information from cortex is transferred to the hippocampal system. During recall (b) and (c), a neocortical event serves to evoke an overlapping pattern of neural activation in the MTL (the blue dots). The hippocampal system responds by activating neocortical regions that provide the experience of recall of some part of the original event. *Source*: Gluck *et al*., 2003.

original episodic experience, or something very much like it. However, this still leaves many questions unanswered, such as, what is the relationship between the electrical stimulus and the normal process of episodic memory retrieval? Why are such extremely specific memories evoked under these circumstances, among the many millions of episodes the average person has experienced? Is there perhaps a relationship between the electrical stimulus and the oscillatory EEG phenomena that are observed in connection with retrieval, like the theta rhythms that seem to coordinate MTL-neocortical retrieval (see below)? Episodic memories reported by patients in neurosurgery after electrical stimulation are fascinating, and appear to be robust and reliable phenomena. But we do not have a good specific explanation as yet.

3.2 Long-term potentiation and long-term depression: excitatory and inhibitory memory traces

Most synapses in cortex are excitatory, using the neurotransmitter *glutamate* (see Chapter 3). A very large minority use inhibitory neurotransmitters like *GABA* (gamma-aminobutyric acid). To encode long-term memory traces in changed synaptic efficiency, these excitatory and inhibitory connections must somehow be made more permanent. These two processes are believed to occur in what is called long-term potentiation (LTP) for excitatory synapses and long-term depression (LTD) for inhibitory ones. These events, which have been observed in specific regions, are simply an increase and a decrease in the firing probability of a postsynaptic potential given a presynaptic spike.

LTP has been observed within the hippocampus itself, using single-cell recording in one of the neuronal layers of the hippocampus (Figure 9.15). Single-cell recording has been extensively done in animals, but there are cases of such recordings in human epileptic patients as well (Kreiman *et al*., 2002).

While we can observe LTP and LTD in specific locations like the hippocampus, the standard hypothesis about long-term memory involves billions of synapses in cortex and its satellites, amounting to literally trillions of synapses. We have no way of taking a census of all of the synapses in this system, or even a substantial fraction of them, at this time. Rather, we have a

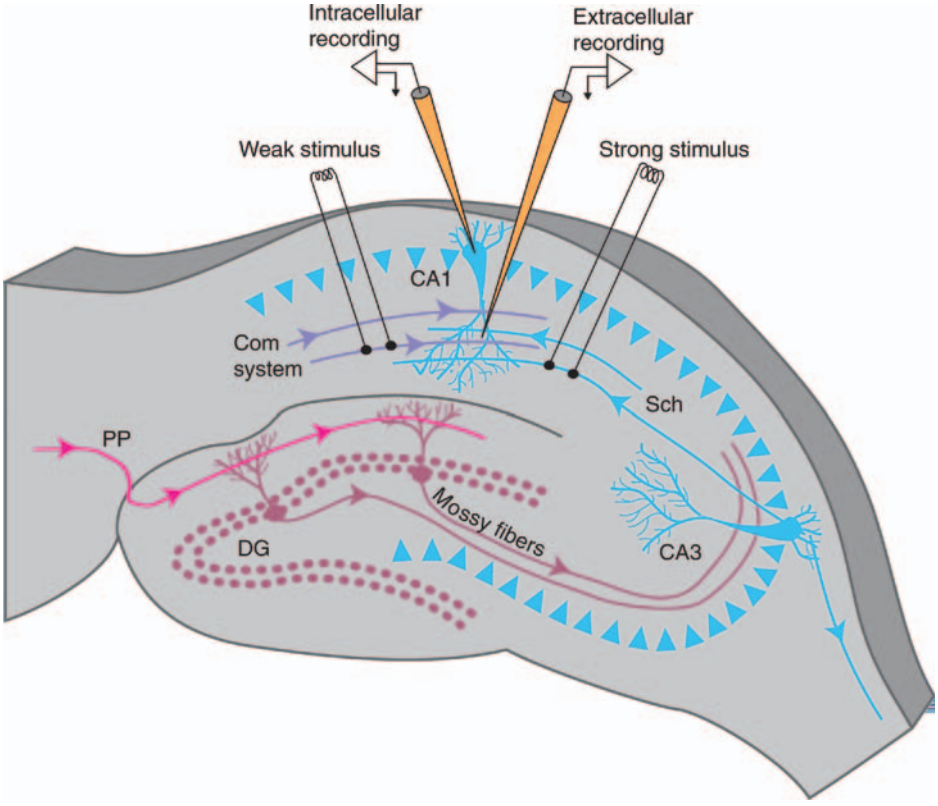


FIGURE 9.15 Single-cell recording in hippocampus. A schematic of single cell recording and stimulation either inside of hippocampal neurons or outside. An electrode placed outside of a neuron can pick up electrical field potentials, which are similar to EEG but much more localized. Electrical field potentials often reflect the activity of small populations of neurons, as opposed to the axonal or dendritic potential of a single neuron. Notice that a very similar technique can be used to stimulate single cells, or small sets of cells, in the hippocampus. *Source*: Squire *et al*., 2003.

number of studies showing increased LTP and LTD in experiments like the one described in Figure 9.16, supplemented by studies of brain damage and of population activity among billions of neurons as measured by EEG, ERP, fMRI, and so on. In addition, we have evidence from stimulation studies, like temporal lobe stimulation of awake patients during neurosurgery, and transcranial magnetic stimulation (TMS) in normal subjects. What we know about memory is therefore an inferential picture, in which many hundreds of studies have been performed. But we cannot yet come close to observing large numbers of changed synaptic connectivities directly at the submicroscopic level.

With that caution in mind, there is good agreement today that the evidence is consistent with these propositions:

1 Episodic input is initially represented via neocortex.
2 It is integrated for memory purposes in the MTL, containing the hippocampi and related structures, and perhaps also the thalamus and surrounding regions.
3 Consolidation: MTL and related regions then bind and integrate a number of neocortical regions, a process that transforms temporary synaptic connectivities into longer-lasting memory traces in both MTL and neocortex. The main mechanism for such changes is believed to be LTP and LTD.

We focus on the last point next.

3.3 Consolidation: from temporary to permanent storage

We can now add the final steps. Chapter 2 suggested a widely accepted hypothesis about the relationship

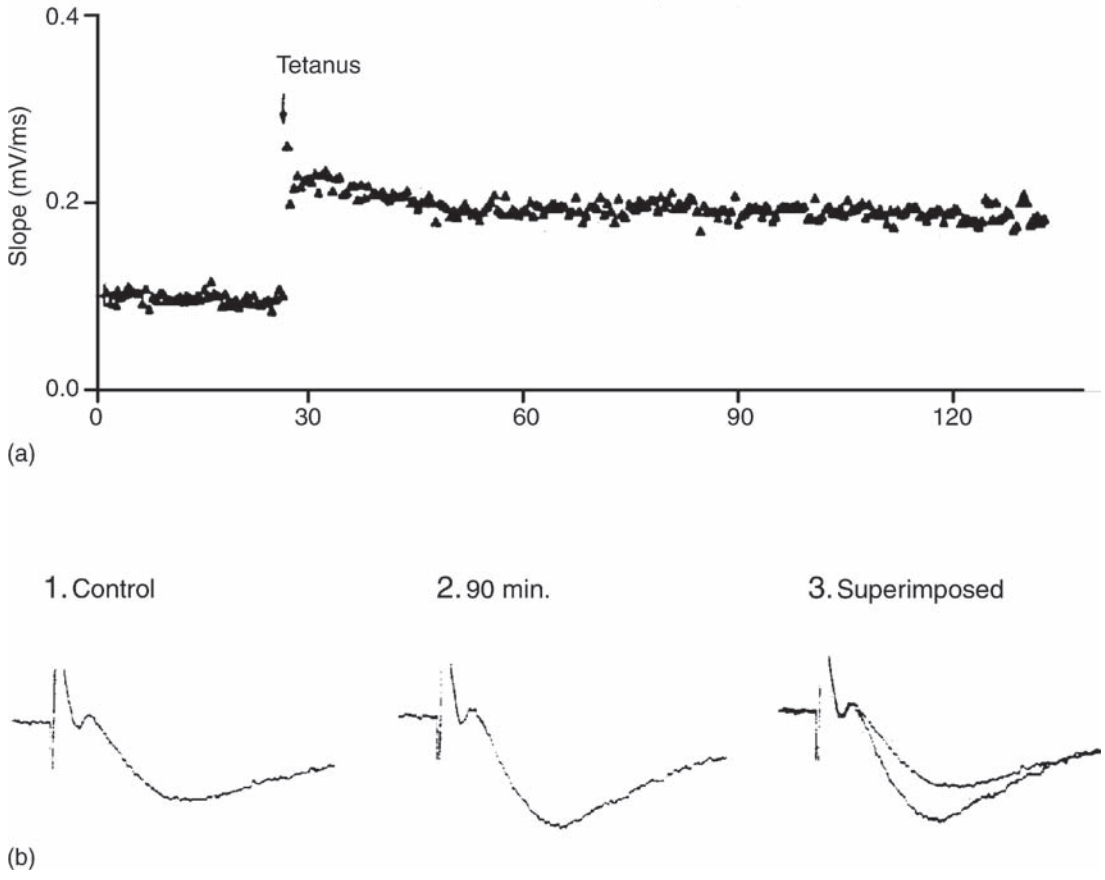


FIGURE 9.16 Long-term potentiation in the hippocampus. Memory traces are believed to be encoded in changed synaptic efficiency among billions of neurons in the neocortex and MTL. These are called long-term potentiation (LTP), corresponding to a permanent increase in excitatory transmission, and long-term depression (LTD), a permanent increase in inhibitory neurotransmission. Direct evidence for LTP has been obtained in hippocampal single cell recordings, as shown above. The lower half of the diagram shows three cases of changed EPSP (excitatory postsynaptic potentials) after strong electrical stimulation presynaptically (called tetanus). Notice that after 90 minutes, the EPSP dips more deeply (remember that a more negative potential means more electrical spiking activity). The graph above shows a long-lasting change in the conductivity of the synapse, as measured by the slope of the EPSPs for 2 hours after the strong electrical stimulus (tetanus). *Source*: Byrne in Squire *et al.*, 2003.

between immediate memory and long-term memory called the *consolidation hypothesis*. Consolidation is generally defined as a progressive stabilization of long-term memory traces so that they are relatively resistant to decay or disruption. It is this process which is absent or severely disrupted in amnesic patients and accounts for their poor ability to transfer information from short- to long-term memory.

Figure 9.17 shows one version of learning with consolidation, in which input into the neocortex and the hippocampal regions (MTL) evoke an active state, with neuronal processes making new synaptic connections. As mentioned above, immediate memory is encoded in improved synaptic connectivity between billions of neurons in the neocortex. Normal sleep, especially the slow-wave stage, is important to turn these temporary connectivities into long-lasting memory traces.

However, more permanent memories are believed to require protein synthesis – such as the growth of dendritic spikes, tiny stalks that grow on top of axons and dendrites, bearing new synaptic connections with neighboring neurons.

The idea that new learning takes some time to 'fix' is quite old. In 1904, Burnham wrote that:

> The fixing of an impression depends on a physiological process. It takes time for an impression to become so fixed that it can be reproduced after a long interval; for it to become part of the permanent store of memory considerable time may be necessary. This we may suppose is not merely a process of making a permanent impression upon the nerve cells, but also a process of association, of organization of the new impressions with the old ones (quoted by Moscovitch).

Figure 9.18 shows these two kinds of consolidation conceptually. The LTP-LTD process discussed above involves cellular consolidation, a local change of connective efficiency in trillions of synapses. However, there is also believed to be *systems consolidation*, in which large-scale reorganization of memories may occur. There is considerable evidence that different sleep stages may have different effects upon this systems consolidation process. Notice that both types of consolidations are thought to involve an active dialogue between the MTL (hippocampus) and neocortex.

3.4 Rapid consolidation: synaptic mechanisms, gene transcription, and protein synthesis

Rapid or synaptic consolidation is accomplished within the first minutes to hours after learning occurs. Weiler and colleagues (Weiler *et al.*, 1995) showed that it correlates with morphological changes in the synapse itself. Stimulus presentation initiates a cascade of neurochemical events at the synaptic membrane and within the cell which increase the synaptic strength or efficiency with which neurons that form the memory trace can communicate with one another. The first of these processes involves local, transient molecular modifications

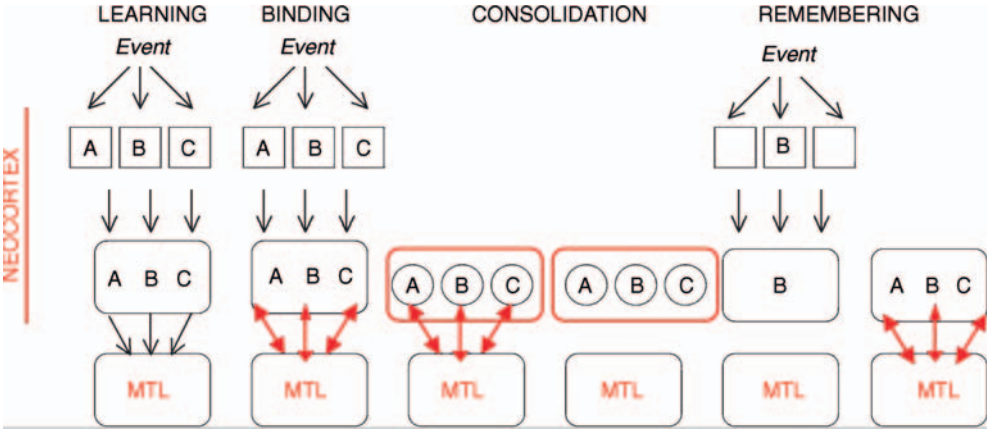


FIGURE 9.17 The steps of learning, binding, consolidation, and remembering. In this summary, Step 1 is the learning of an event, consisting of three elements, A, B, and C. It is initially encoded by neocortex (such as the visual cortex) and sent to MTL. In Step 2, MTL and neocortex resonate with each other to begin establishing the memory trace. In Step 3, the stimulus event is no longer available, and the MTL-neocortical resonance is now independent of external support. Step 4 shows how consolidation leads to permanent, separate memory traces (synaptic changes) in both the MTL and neocortex, which now exist separately from each other, while other input is being processed. In Step 5, element B of the original event (A-B-C) is presented as a reminder or recall cue. In Step 6, the memory traces of A-B-C are activated by resonating activity between MTL and neocortex. At this point, the episodic memory has been retrieved in the absence of the original stimulus. *Source*: Morris Moscovitch, modified with permission.

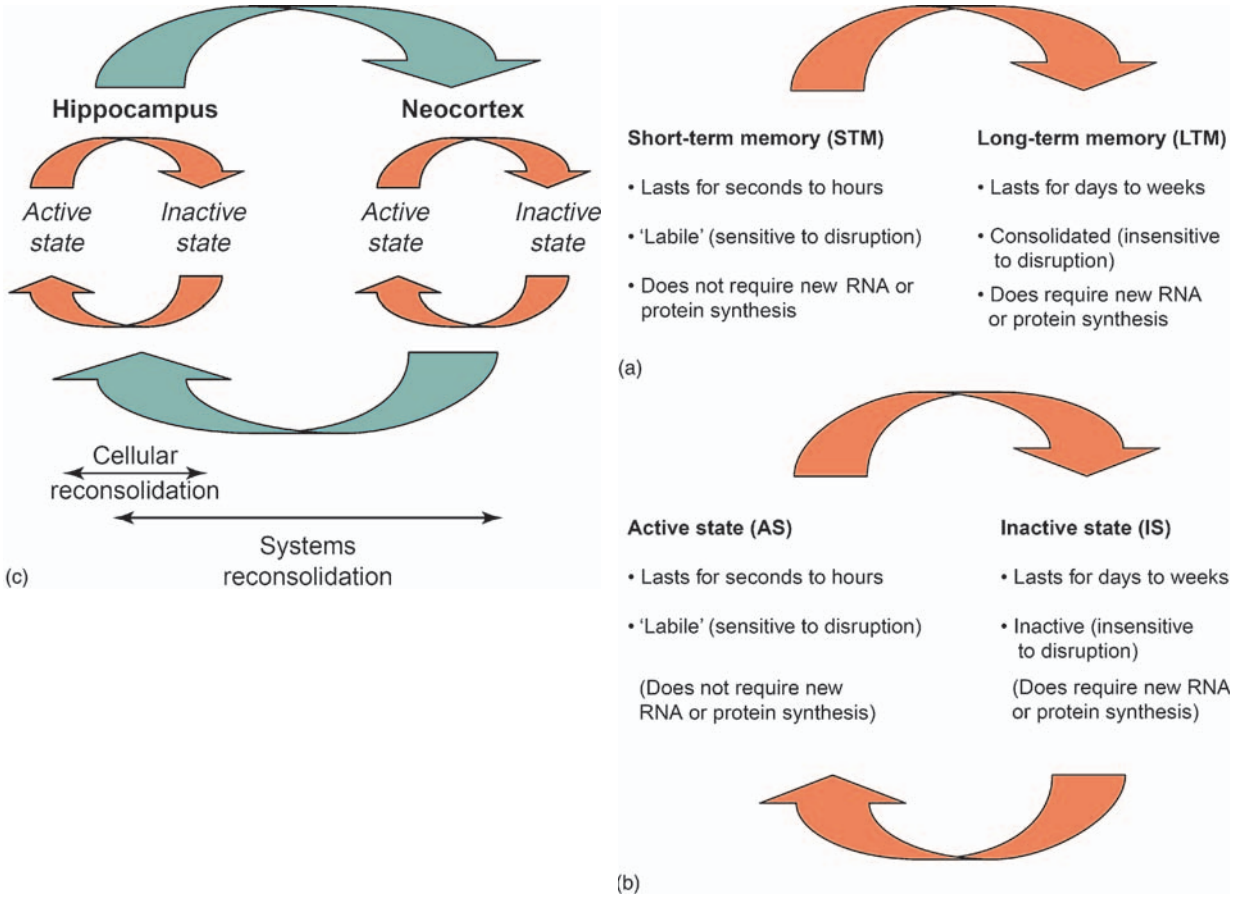


FIGURE 9.18 Reconsolidation turns active neuronal connections into lasting ones. Two kinds of consolidation are believed to exist, cellular and systems consolidation. Both are evoked by activation of MTL and neocortex. This diagram emphasizes the degree to which MTL (also called the hippocampal complex) and neocortex establish active cell assemblies corresponding to the learned input, in which neurons resonate with each other until more permanent connections are established. *Source*: Nader, 2003.

that lead to an increase in neurotransmitter release at the affected synapse. If the stimulus is intense enough and/or repeated, additional processes are activated. These involve gene transcription and protein formation that lead to long-lasting cellular changes, including the creation of new synapses, that support the formation and maintenance of long-term memory. These processes may last from hours to days (Figure 9.19) (Lees *et al.*, 2000; McGaugh, 2000; Dudai, 2004).

Though we are well on our way to understanding the basic cellular and molecular mechanisms of synaptic consolidation, we are far from understanding prolonged or system consolidation, which is being debated heatedly in the literature.

3.5 System consolidation: interaction between the medial temporal lobes and neocortex

System consolidation can take much longer to complete and may range from days to years or decades. Patients with MTL lesions show a retrograde memory loss that is temporally graded, so that recent memory loss (before the amnesia) is greater than earlier memory loss. This temporal gradient is restricted to explicit memory, leaving implicit memory intact and stable over time (Scoville and Milner, 1957).

These observations suggest that the MTL forms a temporary memory trace needed for explicit memories until they are consolidated elsewhere in the brain, presumably in the neocortex (Squire, 1992; Squire and Alvarez, 1995). This standard model of consolidation makes no distinction between various types of explicit memory. For instance, it predicts a similar pattern for episodic and semantic memory.

Nadel and Moscovitch concluded, contrary to the standard consolidation model, that MTL is needed to represent even old episodic memories for as long as the memory exists (Nadel and Moscovitch, 1997, 1998; Moscovitch and Nadel, 1998; Nadel *et al.*, 2000). Neocortex, on the other hand, is sufficient to represent

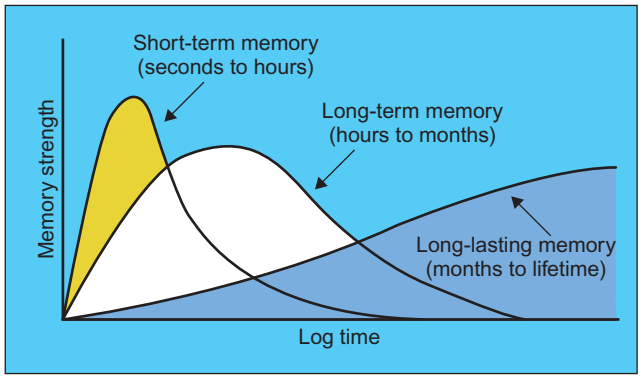


FIGURE 9.19 The time course of consolidation. McGaugh (2000) suggests that there are three overlapping time courses for consolidation. The fastest is referred to as 'short-term memory', from seconds to hours. Long-term memory consolidation takes place over hours to months. Finally, long-lasting memory is needed to account for certain facts, such as the retained long-term memory of early life events in amnesics, who do not have spared memory for some years before brain damage occurred, and none for the time afterward. *Source*: McGaugh, 2000.

repeated experiences with words, objects, people, and environments. MTL may aid in the initial formation of these neocortical traces, but once formed they can exist on their own. Thus, unique autobiographical memories are different from repeated memories, in that they continue to require MTL. Repeated experiences are proposed to create multiple traces, adding more traces each time the event is brought to mind.

Neuroimaging studies provide evidence for this interpretation (Box 9.2). These studies found that the hippocampus is activated equally during retrieval of recent and remote autobiographical memories (Conway *et al*., 1999; Ryan *et al*., 2000; Gilboa *et al*., 2004; for review see Maguire, 2000; Moscovitch *et al*., 2005, 2006). These questions continue to be debated at this time.

4.0 VARIETIES OF MEMORY

Memory is not unitary. Clive Wearing's memory for specific past events in his life is almost entirely destroyed, but he can maintain active knowledge of the immediate past for about 7 seconds (if he is not distracted). Clearly, some forms of memory have been targeted by his disorder and others not. This pattern is routine in amnesic patients, and suggests that different types of memory have different neural underpinnings. A standard view of the major long-term memory systems is shown in Figure 9.20. However, the exact relationship between memory types is still a matter of debate. For example, perceptual memory is classified under non-declarative memory, but this is rather arbitrary. Perceptual memory manifests in an improvement in sensory discrimination at the cortical level, often by reorganization of cortical receptive fields. The result is a change in conscious perception, as in learning to identify clearly the sound of a guitar in music. This has much in common with episodic memory, which can also be largely perceptual and which is generally believed to be conscious. Nevertheless, the memory classification shown in Figure 9.20 is widely used, and is part of the vocabulary students of the field are expected to know.

BOX 9.2 Multiple trace theory versus traditional consolidation

Nadel and Moscovitch (1997) proposed a *multiple trace theory*, suggesting that the hippocampal complex rapidly encodes all information that becomes conscious. MTL binds the neocortical neurons that represent the conscious experience into a memory trace. MTL neurons act as a pointer, or *index*, to the neocortical ensemble of neurons that represent the experience (Teyler and DiScenna, 1986). A memory trace of an episode, therefore, consists of a bound ensemble of neocortical *and* MTL neurons. Formation of these traces is relatively rapid, lasting on the order of seconds or at most days (Moscovitch, 1995).

In this model, there is no prolonged consolidation process that slowly strengthens the neocortical memory trace. Instead, each time an old memory is retrieved, a new hippocampally-mediated trace is created, so that old memories are represented by more traces than new ones, and therefore are less susceptible to disruption. Because the memory trace is distributed in the MTL, the extent and severity of retrograde amnesia is related to the amount and location of damage to the MTL.

While each autobiographical memory trace is unique, the existence of many related traces facilitates retrieval. Episodic memories are integrated to form semantic memories. Thus, facts about people and events that are learned in specific episodes become separated from their sources. This process may give the appearance of classical consolidation, but the brain mechanism is different from the classical view.

4.1 Episodic and semantic memory: 'remembering' versus 'knowing'

As Figure 9.20 shows, declarative memory can be divided into two types, *episodic* and *semantic* (Tulving, 1972). *Episodic memory* refers to memories that have a specific source in time, space, and life circumstances. Episodic memories are often autobiographical in nature, in that we can travel mentally back in time to relive

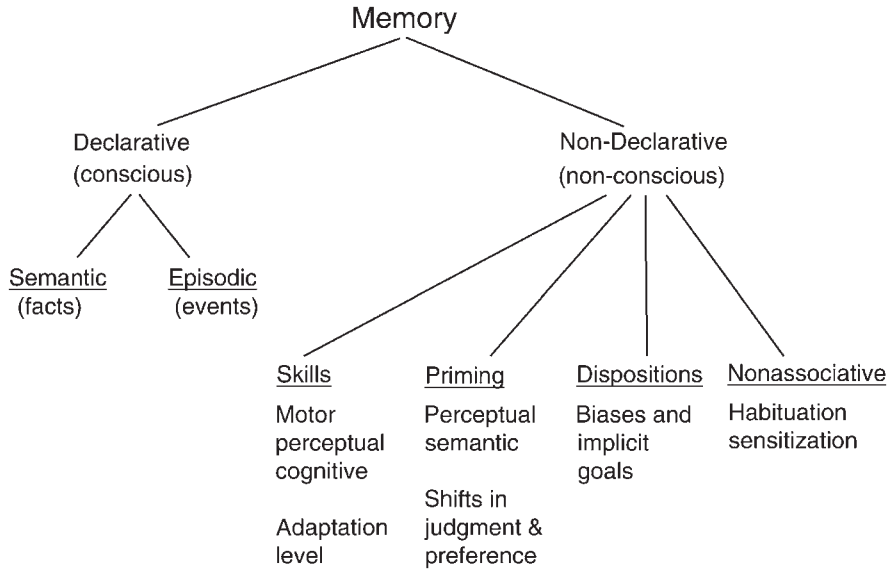


FIGURE 9.20 A classification of memory types. Schacter and Tulving proposed this classification of memory types. Declarative memories have been studied in great detail, and are believed to be explicit (conscious). Non-declarative memory types are said to be unconscious or implicit, but this claim is still debated. While the non-declarative memory types in this diagram undoubtedly have unconscious aspects, it is not yet clear that they can be learned without conscious input. *Source*: Squire, 2004.

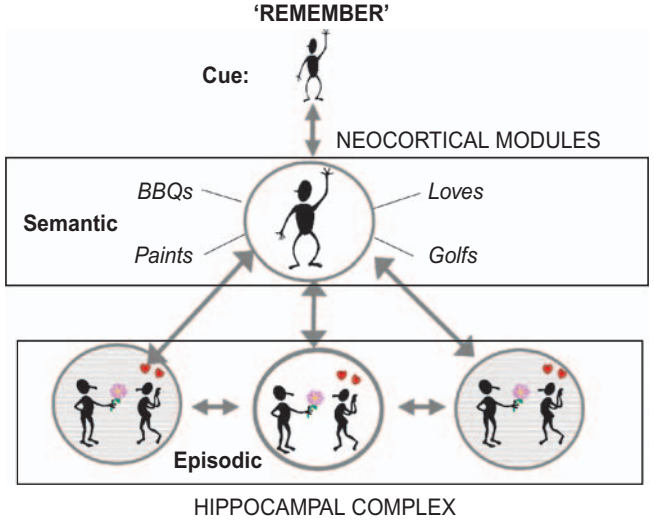


FIGURE 9.21 Remembering: autobiographical episodes. Remembering involves an active reconstruction of the original (conscious) episode. These conscious recollections seem to require hippocampal activity. *Source*: Morris Moscovitch, with permission.

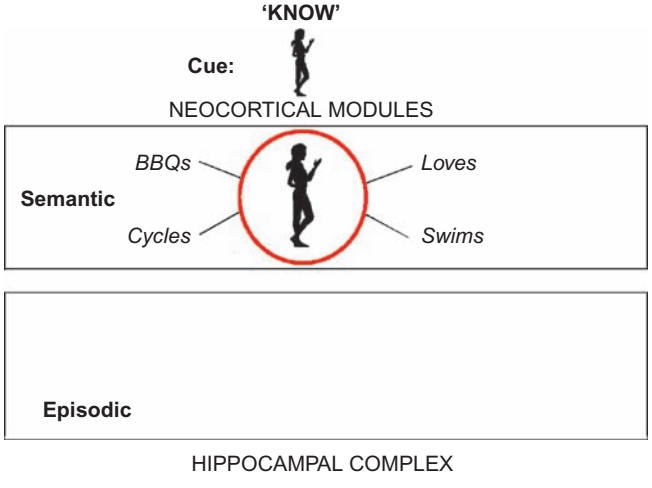


FIGURE 9.22 Knowing: semantic information. Semantic memories are assessed by feelings of knowing, which can be very accurate. However, they do not require active reconstruction of the original episode, and can apparently be accomplished by neocortex without the aid of the hippocampal complex. *Source*: Morris Moscovitch, with permission.

the experience. By contrast, *semantic memories* involve facts about the world, about ourselves, and about other knowledge that we share with a community. Semantic memories are independent of the spatial and temporal context in which they were acquired. A semantic memory may refer to our knowledge of Paris as the capital of France, or Ottawa as the capital of Canada, or the knowledge that we attended a particular high school. By comparison, episodic memory may refer to an event that we experienced in Paris, Ottawa, or high school (Figure 9.21). We often have an autobiographical *source memory* about a specific time, place, and set of circumstances when our episodic memory was acquired. The terms 'episodic' and 'autobiographical' memory are near synonyms.

Episodic memories typically:

1. have reference to oneself
2. are organized around a specific time period

BOX 9.3 False feelings of familiarity: AKP, a person with déjà vecu

People can falsely believe they have known something before when they have not. AKP was an 80-year-old Polish immigrant to Britain, a retired engineer who had a master's degree in his field. He presented to his family doctor with memory problems, and complaining of frequent sensations of what his wife described as déjà vu (actually, déjà vecu, the feeling of having lived through the same experience before). The sensation of déjà vecu was so strong that it influenced AKP's daily activities. He refused to read the newspaper or watch television because he said he had seen it before. The sensation of déjà vecu was extremely prominent when he went for a walk – AKP complained that it was the same bird in the same tree singing the same song, for instance. He also read car number plates and stated that the drivers must have very regular habits always passing by at the exact same time every day. When shopping, AKP would say that it was unnecessary to purchase certain items, because he had bought the item the day before. There was also further evidence of confabulation, including the belief that he had been married three times to the same woman, with three different ceremonies around Europe.

On formal testing, AKP had an above average IQ, scoring above the 90th percentile on some of the subtests. He scored poorly on some, but not all, tests of frontal function. His scores on standardized memory tests, however, were impaired, as were his scores on laboratory tests. Consistent with his condition, he would mistake the lures for targets. As in real life, he not only found new events familiar, but actually believed that he experienced them before.

Structural neuroimaging revealed atrophy of the medial temporal lobes but frontal lobes that appeared normal. Metabolic measures also showed only medial temporal abnormality. This medial temporal abnormality may cause 'memory' signals to be emitted continuously which tag ongoing perceptions as memories.

3 are *remembered* consciously, in such as way that we seem to be able to re-experience them
4 are susceptible to forgetting
5 are context-dependent, with respect to time, space, relationships with others, and other circumstances.

In contrast, semantic memories (Figure 9.22) generally:

1 have reference to shared knowledge with others
2 are not organized around a specific time period
3 give a '*feeling of knowing*' rather than a fully conscious recollection of the original event
4 are less susceptible to forgetting than specific episodes
5 are relatively independent of context.

To investigate the types of consciousness in memory tasks, Tulving (1985) introduced the remember/know procedure. This involves asking participants to introspect about their conscious experience when they recognize studied items. If they believe an item was studied before, they must decide whether they *remember* the item (i.e. they can re-experience episodic details about the event) or whether they *know* the item (it feels familiar) (see Figure 9.23). Local hippocampus seems to affect only 'remember' judgments. Memory based on feelings of knowing is spared (Moscovitch and McAndrews, 2002; Yonelinas, 2002). Similarly, in functional neuroimaging studies, hippocampal activation is associated more with remembering than familiarity (Eldridge *et al*., 2002; Yonelinas *et al*., 2005).

Thus, the hippocampally mediated memory trace is suffused with the consciousness that accompanied the original experience, or what Tulving called *autonoetic consciousness*. This is contrasted with simply having a sense of familiarity about an event, which Tulving refers this as *noetic consciousness*. Noetic consciousness is associated with semantic memory.

4.2 Episodic memories may turn into semantic memories over time

In 1958, Penfield and Milner wrote that:

> The record of the stream of consciousness . . . depends upon the integrity of the bilateral hippocampal structures. . . . Later on, a person deals with what may be called generalizations, and he can summon them to his purposes. All events, even 'memorable' ones, slip away from the reach of voluntary recall unless he has talked about them or preserved them by reflective reconsideration. For example, one remembers a song or a poem that one has heard repeatedly, forgets each hearing or reading, but remembers the generalization. (p. 494)

More than five decades later many memory scientists would agree. There is good evidence that semantic memories may be formed from repeated, similar episodes. Attending a high school is a long series of episodes. We may be able to recall dozens of those episodes, but much of the time they seem 'smeared' together in memory in the semantic belief that 'I attended such-and-such high school'.

Figure 9.24 shows how episodic and semantic memories may be related in the brain. Specific episodic memories are shown in the cartoon below: a

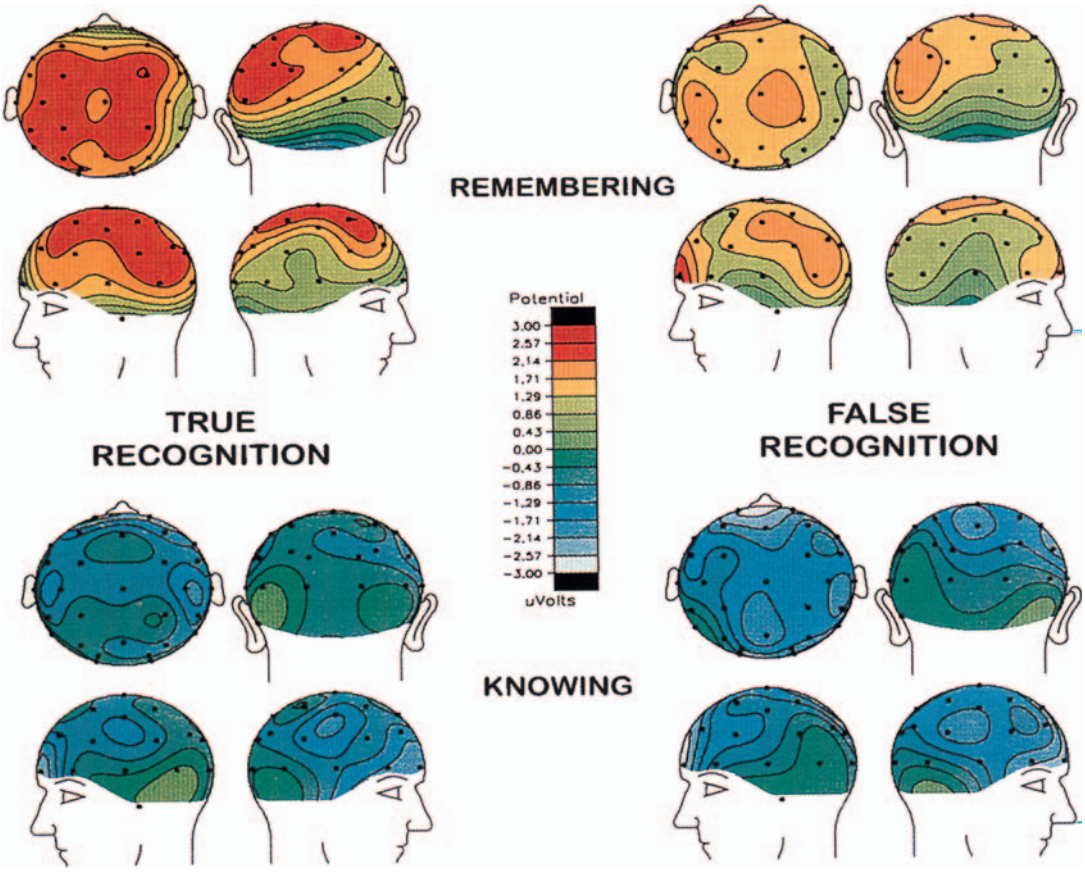


FIGURE 9.23 Even-related potentials for remembering versus knowing. The act of remembering (recollecting the original experience) results in much higher brain activation than the 'feeling of knowing', even for the same material. These brain images involve event-related potentials, scalp EEG traces averaged over trials. This is consistent with evidence discussed in Chapter 8 indicating that conscious stimuli evoked widespread forward activity, outside of sensory cortices, while unconscious stimuli evoke purely local activity. Recollecting original experiences may involve more consciously retrieved material, and it may also require more mental effort, which evokes high activity in prefrontal cortex (see Chapters 10, 11, and 12). *Source*: Duzel *et al.*, 1997.

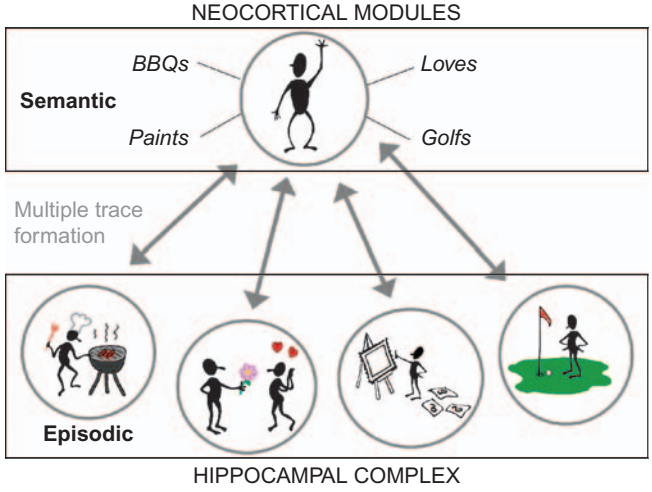


FIGURE 9.24 How semantic and episodic memories may be related: semantic memories may be the neocortical residue of many episodic memories. Thus one may have many experiences with the stick figure above, such as watching him or her cooking a barbecue, presenting flowers to a young lady, painting, and playing golf. Over time, these episodes may be forgotten, and only the semantic knowledge remains, that this is the kind of person who does all those things. These are multiple traces, created each time there is another episodic experience with this person. Semantic memory may require only neocortex (particularly temporal and frontal lobes). Episodic information may require both neocortex and the hippocampal complex. *Source*: Moscovitch, 2004, modified with permission.

man cooking on a barbecue grill, presenting flowers to a young lady, painting a picture, and playing golf. These are separate autobiographical memories, remembered as conscious events. Above, a small semantic network combines all these very specific and richly detailed episodes into a single figure: a semantic network of a man who BBQs, loves, paints and plays golf. The semantic network is more abstract and general than the episodes about particular events in the life of the person. Moscovitch (2004) claims that the bottom row of episodes depends upon the MTL, and the top figure depends upon neocortical modules.

We can summarize this concept in three steps:

1. Initially, memories are episodic and context-dependent
2. Over time, episodic memories are transformed into semantic memories
3. MTL is important for recovering episodic memories, which are linked to the specific autobiographical context in which they were acquired.

In this view, the hippocampal complex or MTL supports:

1. Storage and retrieval of detailed, remote autobiographical and spatial memories
2. Formation and assimilation of semantic memory in neocortex.

4.3 Episodic and semantic memory are often combined

When you are asked if the face of a particular person is familiar to you, say, the movie star Brad Pitt, on what basis are you making your judgment? Are you relying on your semantic memory, episodic memory, or both? Westmacott *et al*. (2004) have shown that *both* systems may contribute, because performance on semantic tests is better if the participant also has some episodic memory associated with the famous name.

Semantic dementia is diagnosed in a subset of Alzheimer's disease patients who show widespread deficits in understanding meaning, often with spared perceptual abilities. These patients, whose degeneration of anterior and lateral temporal lobes leads to semantic loss, can identify common objects only if they can make a personal association to them. For example, they can identify a vase if it belongs to them, but not any other vase (Snowden *et al*., 1996; Graham *et al*., 1999).

Remarkably, however, if MTL is injured very early in development, during infancy, semantic memory develops relatively normally in most cases (Vargha-Khadem and Mishkin, 1997). However, episodic memory still remains impaired without an MTL. What these findings suggest is that early in life, the semantic system has the capacity to acquire knowledge on its own, without the help of the episodic system (MTL).

5.0 MTL IN EXPLICIT LEARNING AND MEMORY

MTL is necessary for conscious recollection of long-term, episodic memories. We do not have a way voluntarily to 'switch on' our MTL. Rather, all we need to do is to pay attention to some material we want to memorize. As pointed out in Chapter 8, that means in most cases that we become conscious of the material, and an episodic memory is apparently established without doing anything more.

That is, conscious experiences, such as the sight of the coffee cup in Figure 9.4, appear to be necessary and sufficient to record a conscious experience, using MTL, assuming of course that we are dealing with an intact brain. The episodic memory trace consists of an ensemble of MTL and neocortical neurons, while the MTL acts as a pointer to the neural elements in neocortex for the event. Retrieval occurs when a conscious cue triggers the MTL, which in turn activates the entire neocortical ensemble associated with it. When we recover episodic memories, we recover conscience experiences (Moscovitch, 1995). The recovery of these consciously experienced events, in rich detail, always depends on the hippocampus no matter how long ago the memory was acquired. As Moscovitch (1992) has argued, the hippocampal complex acts as a module whose domain is consciously apprehended information. Much of the evidence seemed consistent with that view.

Some recent studies, however, have questioned this hypothesis. Using fMRI, Henke and her collaborators (Henke *et al*., 2003; Degonda *et al*., 2005) showed that the hippocampus can be activated by subliminal presentation of faces and their associated professions. Moreover, these activations are correlated with performance on subsequent explicit tests of memory for faces-profession pairs. Likewise, Daselaar *et al*. (2006) found that the posterior medial temporal lobe was activated more by old, studied items at retrieval, even when the person was not aware that the item was old. Finally, Schedon *et al*. (2003) showed that the hippocampus was activated on the SRT task if the repeated sequences were of a higher order of association.

There also have been similar reports from studies with amnesic patients. Ostergaard (1987) was the first

to suggest that performance on some priming tests was related to the extent of medial temporal damage. More recently, Chun and Phelps (1999) showed that non-conscious context effects in visual search were not found in amnesic patients, suggesting that the MTL was needed for retaining contextual information of which the person was not aware. Likewise, Ryan and Cohen (Ryan *et al*., 2000) showed that amnesic people did not show the normal pattern of eye movements around the location where a change occurred in a studied picture, even though neither they nor the normal people were consciously aware of the change.

These are a handful of studies in an armful of older studies which claimed that the hippocampus is associated only with explicit memory. If the recent studies are replicated and not found wanting, then it would change our ideas about the relation of the hippocampus to consciousness and memory.

5.1 Divided attention interferes with learning

Learning works best when you pay attention. Trying to study in an environment where lots of other interesting things are happening is not likely to work. Psychologists have used this 'divided attention' or 'dual task' technique to understand the contribution of attention (or consciousness) to memory. In a typical study, participants are asked to process target material, such as words or pictures, while at the same time their attention is diverted with another task, such as tracking a dot on the screen, or deciding whether a running count of digits contains three successive odd numbers. Under such conditions, even if the participant is given a task that requires in-depth, meaningful analysis of the material, memory under divided attention is much worse than memory under full attention. Successful encoding requires a level of attention and presumably consciousness.

Exactly why that is the case is not well understood. One possibility is that deeper processing requires time to complete, and divided attention limits the time allotted to encoding. Another possibility is that consciousness or awareness is a necessary contributor to memory. If one is not fully conscious of the processed material, no matter how deeply it was processed, memory will suffer accordingly. A third possibility is that attention limits elaboration or organization, both of which contribute to good memory.

Fletcher *et al*. (1995) found, in a PET study, that activation of the left inferior prefrontal region is reduced under divided attention. This finding was replicated by Anderson *et al*. (2000) in younger and older adults, with the additional observation that divided attention also reduced activity in the left medial temporal lobes, regions known to be important for verbal memory.

Memory and learning have both conscious and unconscious aspects. If we think about three phases – learning, retention, and retrieval – we can lay out the possibilities in a 3×4 matrix (Table 9.1). Of the three, retention is generally viewed as unconscious, although it is shaped by conscious experiences. Learning is often thought to require consciousness and, intuitively, we certainly try to learn things by paying attention and becoming conscious of what we need to learn. That is perhaps the basic learning strategy we have as human beings.

However, there is some evidence for learning without consciousness, especially in the case of emotional stimuli. There is much stronger evidence for implicit learning, in which some inferential process takes conscious input and encodes unconscious results of conscious input. However, implicit learning tasks always ask subjects to pay attention and become conscious of a set of stimuli (Section 2.4). It is the rules and regularities that generate those stimuli that are learned without consciousness, just as we normally learn the rules of linguistic grammars without knowing those rules explicitly. But we must hear spoken words and word sequences consciously in order for implicit learning to occur.

The terms implicit and explicit memory are used in the context of remembering, i.e. retrieval of stored information. *Explicit memory* refers to memory with

TABLE 9.1 Some types of learning and memory – explicit and implicit

Type	Learning	Retention	Retrieval
Episodic memory	Conscious or explicit	Unconscious	Conscious or explicit of the learning experience
Semantic memory	Conscious or explicit	Unconscious	Unconscious or implicit for the learning experience
Implicit learning	Conscious stimuli, but unconsciously learned regularities	Unconscious	Unconscious retrieval
Subliminal learning (rarely robust and long term)	Unconscious of target stimuli	Unconscious	Unconscious retrieval

conscious awareness, namely, memory of which the individual is aware, can declare its existence, and comment on its content, either verbally or non-verbally (Schacter, 1987). For this reason, such memories also are known as *declarative memories* (Ryle, 1949; Cohen and Squire, 1980). They are the kind of memory to which we typically refer in everyday conversation when we ask 'Did you remember to call your aunt to thank her for the birthday present?' or 'Do you remember who won the Academy Award for Best Actor or Actress?'

6.0 PREFRONTAL CORTEX, CONSCIOUSNESS, AND WORKING MEMORY

The prefrontal cortex (PFC) plays a critical role in working memory. The prefrontal cortex is situated in front of the motor cortex in both humans and other primates (Figure 9.25). The macaque monkey has been the primary experimental animal in many studies of working memory. Obviously, humans have other abilities, like language, that are not directly paralleled in other species. But, in the case of working memory studies, the macaque has been a constantly important source of evidence.

Knowledge of a link between the PFC and short-term memory dates back to the 1930s, when it was first discovered that large bilateral lesions of the PFC in animals impaired performance on a delayed response task. In this task, a sample stimulus is presented (e.g. a color or location), and its identity must be maintained over a short delay period so that it can guide a later response (Figure 9.26). Using variants of this basic task with more recent neuroscientific techniques, modern research has firmly established the role of the PFC in active maintenance of WM information (Figure 9.27).

Much of the animal research has focused on a specific frontal region called the dorsolateral prefrontal cortex (DL-PFC, see Figure 9.25). (In the human cortex dorsal is 'upper' and lateral means 'to the side'.) One of the key early findings came from the laboratory of Joaquin Fuster (Fuster and Alexander, 1971). Fuster and his colleagues trained monkeys to perform a delayed-response task in which they had to remember a color over a brief delay, and then point to the correct color when later presented with two alternatives. Since no information about the correct color was offered after the initial presentation, its identity had to be retained in working memory. Using implanted electrodes to record neural activity during performance of the task (see Chapter 4), it was found that individual neurons in the monkey DL-PFC exhibited sustained and persistent activity across the delay period. That is, after the color had been removed from the visual display, neurons in the DL-PFC continued to fire at an increased rate, and this activity then subsided once the match/non-match response was made (Figure 9.26).

This pattern of sustained delay-period activity in the DL-PFC has been replicated many times since, and in a wide variety of tasks. For example, to confirm that PFC contributions are truly memory-related, and not simply a reflection of subtle preparatory motor

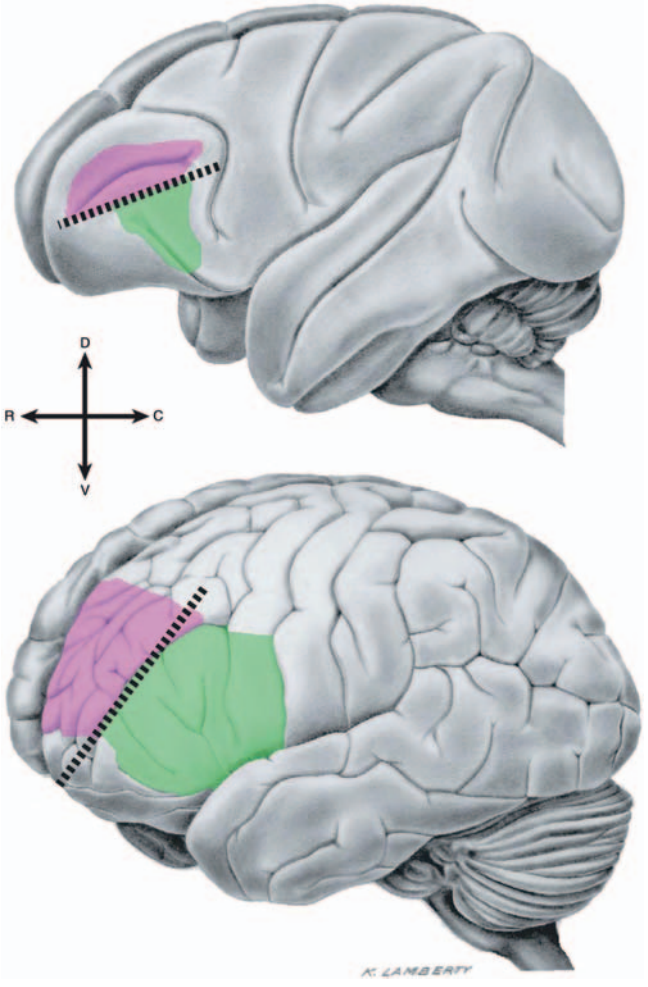


FIGURE 9.25 The prefrontal cortex in monkeys (top) and humans (bottom). The most common division is between upper and lower halves of the prefrontal cortex (PFC), called the dorsolateral prefrontal cortex (DL-PFC) for the light purple region, and the ventrolateral prefrontal cortex (VL-PFC) for the light green area. Also notice the orientation cross, pointing to dorsal (upper), ventral (lower), rostral (toward the nose in humans), and caudal (toward the back of the head in humans). *Source*: Ranganath, 2006.

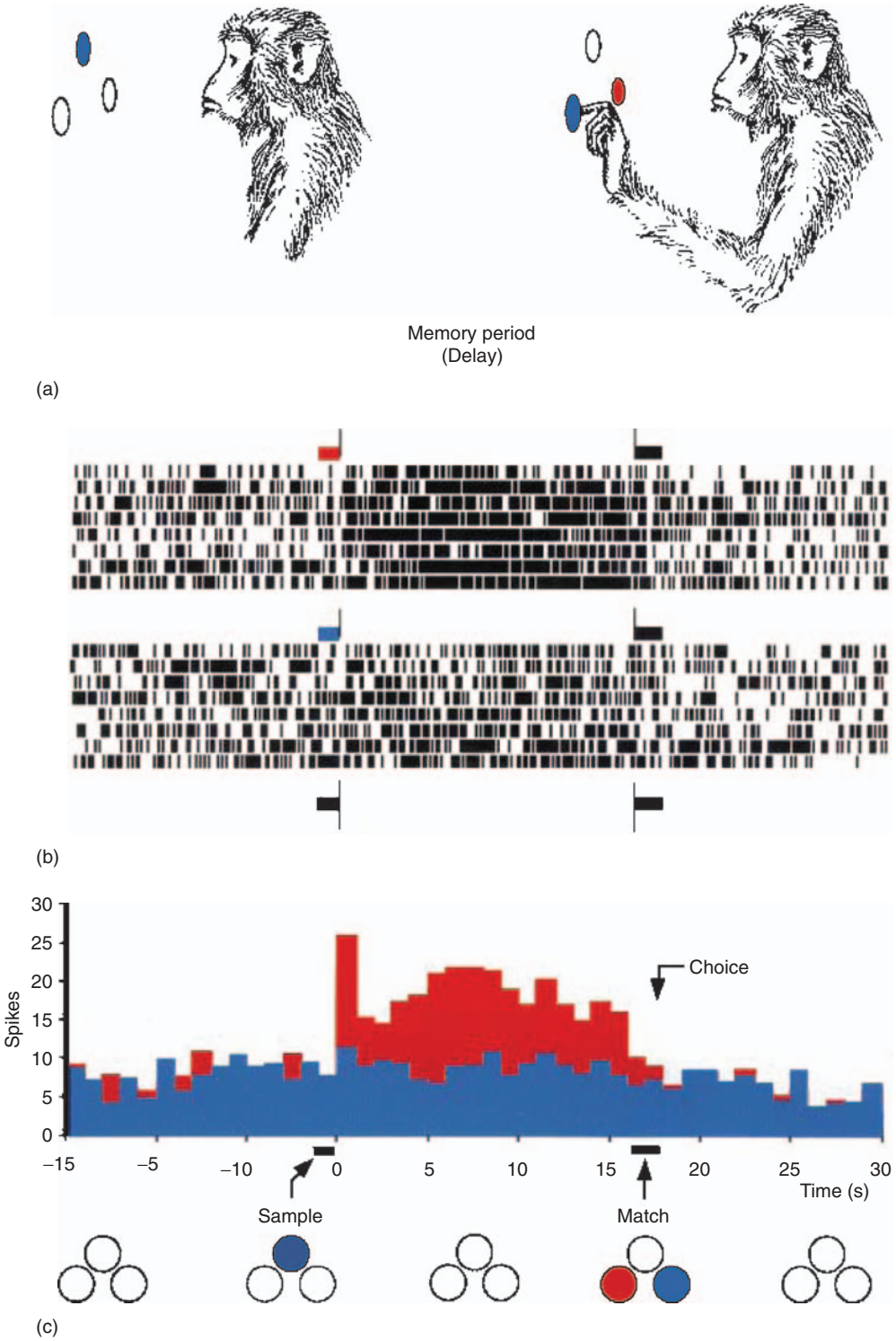


FIGURE 9.26 'Delayed match to sample' in the macaque. In a classic experiment, a macaque monkey is trained to delay responding to a stimulus, in this case the location of a red, white, or blue light. The monkey shows recognition of the stimulus after delay by matching it in the display, in a task called 'delayed match to sample'. In effect, the monkey is communicating 'this is what I saw'. DMTS methods are widely used in animals, non-verbal babies, and other subjects. *Source*: Fuster, 1997.

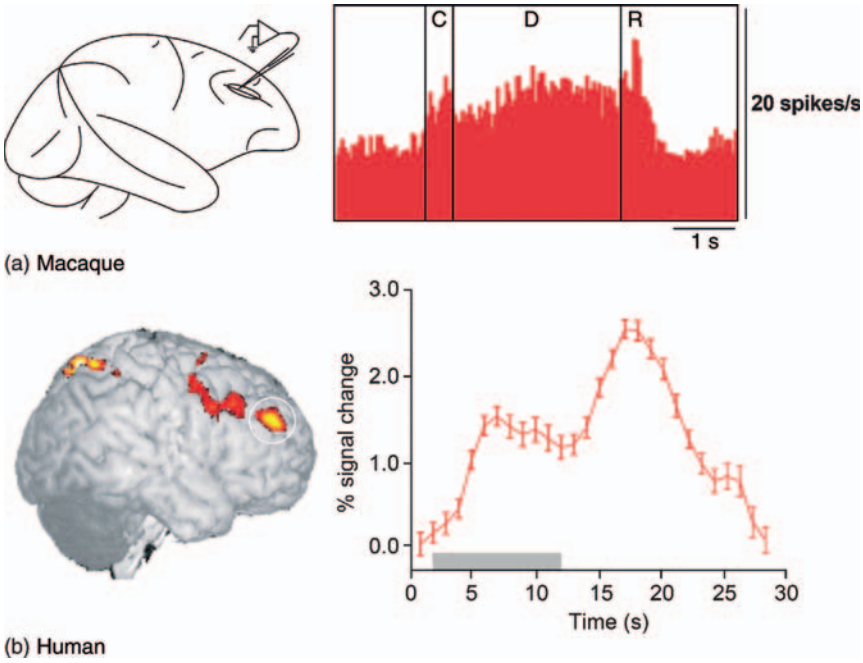


FIGURE 9.27 A delayed-response task to study working memory in monkeys and humans. It has been proposed that the PFC serves a specific role in the active *storage* of information in working memory (e.g. Goldman-Rakic, 1998). That is, sustained activity in prefrontal neurons reflects this region's role in maintaining specific representations of the items that must be kept in mind over the delay. This interpretation is supported by the finding that individual neurons in the PFC are selective for particular target stimuli. For example, a given cell may fire strongly over the delay period when the target is in the upper left portion of the display, but weakly when the target is elsewhere in the display. This pattern suggests direct involvement in the internal representation of target features. In this figure, neurons in prefrontal cortex respond during the delay period in a delayed-match-to-sample task. Results in macaques and humans are similar. *Source*: Curtis and D'Esposito, 2003.

gestures, Patricia Goldman-Rakic and her colleagues developed a version of the task in which monkeys see a target presented briefly at one of several possible locations on a display, and then after a delay, must shift their gaze to that location in order to receive a reward. Importantly, the monkey is required to look straight ahead until the end of the delay period, so neural activity during the delay cannot be simply a byproduct of moving the eye, but must instead reflect memory processes. Again, this paradigm produces sustained neuronal activity in the DL-PFC and, what's more, the *amount* of delay-period activity predicts whether or not items will be remembered; when DL-PFC delay-period activity is weak there is a greater likelihood of forgetting (Funahashi *et al*., 1993).

There is debate whether PFC is subdivided according to the content of the information that is stored or according to the function that each region carries out. According to the content approach, the DL-PFC seems to be particularly involved in holding onto information about spatial locations, whereas different parts of the ventral and lateral PFC have been implicated in storing non-spatial types of information (e.g. objects, faces, words, etc.). Alternatively, each of these regions may have different functions, with DL-PFC implicated in manipulation of information and VL-PFC in maintenance (ventro-lateral, downward and to the side). The term ventral refers to the down direction in cortex; literally, 'ventrum' means 'belly' in Latin.

Monkey brain lesion studies have further implicated the PFC, and the DL-PFC in particular, in working memory function. With very precise techniques for localizing experimentally-induced lesions, it has been shown that damage isolated specifically to the DL-PFC is sufficient to impair performance on working memory tasks (Fuster, 1997). Such findings show a causal role for the PFC in working memory. Not only are cells in this region active during a delay, but their lesioning impairs working memory. This impairment gets worse as the length of the delay increases, suggesting that there is more rapid forgetting when the PFC is prevented from sustaining them.

Studies in humans using neuroimaging have corroborated many of the findings from the animal literature. Hundreds of imaging studies have shown PFC activity when participants are trying to maintain task-relevant information. Consistent with the animal work, fMRI studies in humans show that PFC activity persists during the delay period of a working memory task (see Chapters 4, 10, and 12; and the Appendix).

Human neuroimaging studies have also varied *working memory load* – the number of items that must be held in immediate memory (Cohen *et al*., 1997; Rypma *et al*., 2002). In one study, memory load was varied between one and eight items, and subjects had to hold these items for a short delay. PFC activation was found to be positively correlated with the number of items in memory. Such 'load dependence' in the PFC supports the notion that this part of the brain is involved in working memory storage (See Chapter 12).

While PFC contributions to working memory have been clearly demonstrated, its specific contribution to working memory storage has been recently questioned. Several other cortical and subcortical areas exhibit similarly persistent stimulus-specific activity over short delays. It appears that PFC may be part of a more distributed brain network supporting working memory. Other data suggest that the PFC may not be involved in storage *per se*, but in providing top-down, or *executive*, support to other regions where information is actually stored.

6.1 Working with memory: the frontal lobe works purposefully *with* memory

According to this model, both encoding and retrieval of consciously apprehended information via the hippocampus and related structures is obligatory and automatic, yet we know from experience and from experimental investigation that we have a measure of control over what we encode and what we retrieve from memory. Moreover, if encoding is automatic and obligatory, the information cannot be organized, yet memory appears to have some temporal and thematic organization. How can we reconcile this model of memory with other facts we know about how memory works? One solution is that other structures, particularly those in the frontal lobes, control the information delivered to the medial temporal system at encoding, initiate and guide retrieval, and monitor and help interpret and organize the information that is retrieved. By operating on the medial temporal and diencephalic system, the frontal lobes act as *working-with-memory* structures that control the more automatic medial temporal system and confer a measure of intelligence and direction to it. Such a complementary system is needed if memory is to serve functions other than mere retention and retrieval of past experiences (Moscovitch, 1992).

6.2 Prefrontal cortex in explicit (conscious) and implicit (unconscious) learning and memory

Figure 9.5 pointed out that working memory may help us to learn both explicit (conscious) and implicit (unconscious) information. One of the functions often attributed to consciousness is the integration of information across domains. In a very illuminating study, McIntosh *et al*. (1998) had subjects perform in a trace conditioning task which requires the person to make an association between a color and a tone separated by a blank delay of about a second. Previous work had shown that such conditioning is dependent on the hippocampus. Moreover, Clark and Squire (1999) showed conscious awareness of the association was a prerequisite for this kind of learning.

Using PET, McIntosh showed that learning, and the conscious awareness that accompanied it, was associated both with frontal activation and with coherence of activation across many areas of cortex. McIntosh *et al*. speculated that consciousness is associated with activation in prefrontal cortex which, in turn, leads to a correlated pattern of activity across disparate regions of cortex. It remains to be seen, however, whether frontal activation preceded or followed conscious awareness of the association. To do so, it is necessary to have a clear understanding of the sequence of activation across regions of cortex, using techniques that have a higher temporal resolution than fMRI, such as ERP or MEG. As yet few, if any, studies have used ERP and MEG to address issues regarding the time course of consciousness as it relates to memory.

If the prefrontal cortex plays a pivotal role in consciousness, as many people have speculated, deficits on all memory tests dependent on consciousness should be observed in patients with frontal lesions. However, so far, the evidence indicates that the effects of frontal lesions are much more selective and not nearly as debilitating as lesions to MTL and related nuclei of the thalamus.

The prefrontal cortex contributes to performance on implicit learning and memory if it requires search, sequencing, organization, and deliberate monitoring. Implicit learning of language is a good example

BOX 9.4 Implicit learning of language. While we are given the words and sequences of language, the rules and regularities of grammar and perhaps meaning are often inferred unconsciously, i.e. using implicit learning

Implicit learning and language acquisition

The past few years have witnessed the emergence of increasing connections between implicit learning and psycholinguistics. This is perhaps not so surprising, in that language acquisition, like implicit learning, involves incidental learning conditions. Further, cogent use of language likewise does not require explicit knowledge of grammar. Recently, several authors have begun to explore this connection empirically. For instance, Saffran *et al*., 1997, showed how incidental exposure to artificial language-like auditory material (e.g. *bupadapatubitutibu* . . .) was sufficient to enable both children and adult subjects to segment the continuous sequence of sounds they had heard into the artificial words (e.g. *bupada, patubi*, etc.) that it contained, as evidenced by their above-chance performance in a subsequent recognition test. Based on these data, Saffran *et al*. suggested that the word segmentation abilities demonstrated by these subjects were due to the transitional probabilities of successive syllables are higher *within* words than *between* words. Saffran and colleagues interpreted their findings as representing a form of implicit learning. The connection is obvious when one recognizes that language acquisition, like implicit learning (Berry & Dienes, 1993; Cleeremans, 1993) is likely to involve, at least in part, incidental learning of complex information organized at differing levels. Part of the convergence between language acquisition and implicit learning suggested by Saffran and colleagues can be attributed to the impact of computational modeling on the field of memory research. For instance, connectionist models such as the Simple Recurrent Network have been extensively used with significant success in both the language acquisition and implicit learning domains (Christiansen *et al.*, 1998; Redington & Chater, 1997). In effect, the problems faced in both domains are quite similar: how to best extract structure from a complex stimulus environment characterized by 'deep' systematic regularities when learning is incidental rather than intentional. The answer, in both domains, appears to be embodied by distributional approaches.

References

a Saffran, J. R., *et al.* (1997). Incidental language learning, listening (and learning) out of the corner of your ear. *Psychological Science*, *8*, 101–105.

b Berry, D. C., and Dienes, Z. (1993). *Implicit Learning: Theoretical and Empirical Issues*. London: Erlbaum.

c Cleeremans, A. (1993). *Mechanisms of Implicit Learning: Connectionist Models of Sequence Learning*. Cambridge: MIT Press.

d Christiansen, M. H., Allen, J., and Seidenberg, M. S. (1998). Learning to segment speech using multiple cues: a connectionist model. *Language and Cognitive Processes*, *3*, 221–268.

e Redington, M., and Chater, N. (1997). Probabilistic and distributional approaches to language acquisition. *Trends in Cognitive Sciences*, *1*, 273–281.

(Box 9.4). Even though we rarely try to make the rules of grammar conscious and explicit, we nevertheless need to direct our attention to the order of words in a sentence, for example, to learn a language implicitly. It is likely that unconscious inferences help us to discover rules or regularities, provided that we pay 'conscious attention' to a series of words, for example, from which we can discover the implicit regularities.

6.3 Different types of working memory

In proposing the concept of working memory, Baddeley and colleagues (2004) reasoned that subjects should have difficulty keeping items in memory if asked to perform other tasks simultaneously that disrupt specific components of the working memory system. Consistent with this view, Baddeley and others have shown that asking subjects to repeat aloud a simple utterance (like the word 'the') during retention can dramatically reduce short-term memory for verbal information, presumably because the repetitive speech task disrupts the rehearsal mechanism of the phonological loop. Importantly, the same repetitive speech task has a much smaller effect on working memory for visuospatial information because holding such information does not make as much use of the phonological loop. Meanwhile, other tasks (e.g. visually tracking a moving object) have been found to disrupt visuospatial, but not verbal, maintenance.

We have already encountered examples of patients, like Clive Wearing and HM, who seem to have spared short-term memory but impaired long-term memory. Elizabeth Warrington and Tim Shallice (Shallice and Warrington, 1970) reported one of the earliest recognized cases of a patient, KF, with the opposite pattern of impairment – a severely impaired short-term memory but apparently intact long-term memory. For example, when asked to recall short lists of spoken digits, the *digit-span task*, KF could recall only one or two items reliably (as compared to a typical digit-span of around seven items). Still, KF had comparatively normal speech-production abilities, and could learn and transfer new information into long-term memory. The finding that a patient with severely impaired short-term memory could still transfer information into long-term memory presented a challenge to the

standard hypothesis posited that a unitary short-term memory serves as the gateway into long-term memory. Baddeley's working memory model suggested that if verbal rehearsal is impaired, the visuospatial sketchpad might be used to compensate (see Figure 9.5).

Indeed, the short-term memory impairment in patient KF, and a number of similar patients reported since, seems to be tied to particular types of information. For example, while these patients struggle to remember verbal items when presented auditorily, their performance is considerably improved when the items are presented visually. What might account for this pattern of findings? Baddeley's answer is that visually presented items can be coded directly into the visuospatial sketchpad, thus avoiding the damaged verbal rehearsal loop.

Neuroimaging has helped to clarify different kinds of memory. These include the distinction between verbal and visuospatial maintenance subsystems (e.g. Smith *et al*., 1996), the dissociability of storage and rehearsal in verbal maintenance (Paulesu *et al*., 1993; Awh *et al*., 1996) and the assumption of a central executive processor that mediates the behavior of the subsidiary maintenance subsystems (e.g. Curtis and D'Esposito, 2003). In general, neuroimaging studies have tended to support the basic model (Smith and Jonides, 1998; Hartley and Speer, 2000; Henson, 2001).

Figure 9.28 illustrates the brain network implicated in neuroimaging studies of WM (Curtis and D'Esposito, 2003). The central executive corresponds to DL-PFC (labelled as 'D' on the figure), the verbal maintenance subsystem in left lateralized regions of the temporo-parietal junction (labelled as 'P' on the figure) and VL-PFC, and the visuospatial maintenance subsystem in the superior parietal cortex, posterior PFC, and frontal eye fields (FEF, labelled as 'F' on the figure). However, we should be cautious in our acceptance of these findings as direct support for the framework, since few researchers have considered the applicability of these findings to alternative theories of working memory (Chein *et al*., 2003; Ravizza *et al*., 2005). In addition, the neuroimaging literature has at times challenged aspects of the standard working memory model. For example, neuroimaging evidence suggests that different types of visuospatial information may depend on different storage subsystems. For instance, there seem to be different neural substrates for the maintenance of *object* information as compared to the maintenance of *spatial* locations, a distinction that is not addressed by the traditional working memory model. (Recall that this 'what' versus 'where' dichotomy is important also in the visual processing pathways; see Chapter 6.)

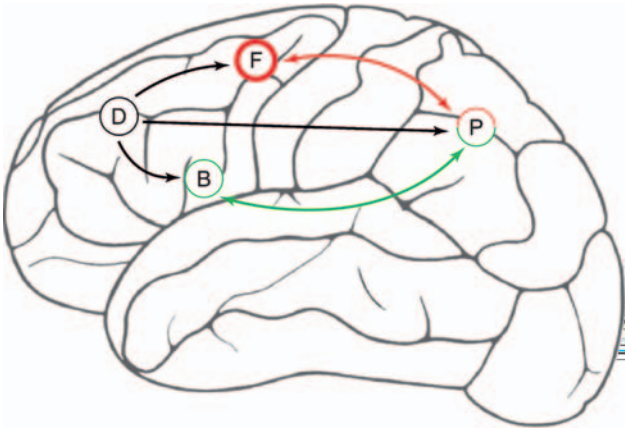


FIGURE 9.28 Brain areas believed to be involved in verbal and visual working memory. A simplified brain model of working memory (Figures 9.4 and 9.5). Abbreviations are D = dorsolateral prefrontal; B = Broca's area, also called the left inferior frontal gyrus (L-IFG); P = phonological loop for verbal rehearsal, also called the supramarginal gyrus; and F = frontal eye fields, believed to be involved in the visuospatial sketchpad of Baddeley's working memory model. *Source*: Curtis and D'Esposito, 2003.

6.4 Prefrontal cortex – storage or process control?

In the beginning of this section on working memory, we reviewed several sources of evidence suggesting that the PFC is an important site for working memory function. According to one interpretation, this brain region participates directly in the storage of information. However, consideration of findings in the context of Baddeley's multiple-component model suggests an alternative account – namely, that the PFC is more closely associated with control, or executive, aspects of working memory.

Specific evidence against a 'storage' interpretation of PFC function also comes from studies of humans. We discussed earlier a group of patients with left temporo-parietal damage who appear to have a storage deficit in working memory, and can't perform even simple maintenance tasks with auditory-verbal information. The findings from these patients can be contrasted with those from patients with damage to the PFC. In a review of published reports from patients with damage to large regions of the lateral PFC (D'Esposito and Postle, 1999), it was found that PFC patients showed little or no impairment on tasks that called for the passive maintenance of information over a delay (e.g. verbal and non-verbal memory span tasks). However, these patients were found to be substantially impaired at tasks that required information

in working memory to be mentally *manipulated* or *acted upon*. This pattern of findings suggests that the PFC serves to support the mental 'work' performed on stored information, rather than as a site for storage itself. Few of the patients in this review had bilateral lesions, leaving open the possibility that storage and rehearsal are achieved via bilateral PFC representations and may thus allow functional compensation from the undamaged hemisphere (D'Esposito and Chen, 2006).

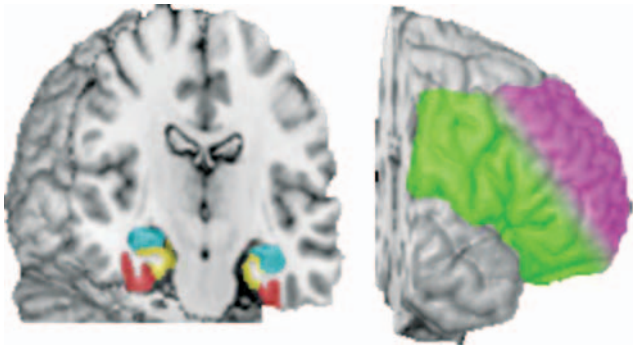
One possibility is that different parts of the PFC do different things. This proposal has generally focused on differences between dorsal (DL-PFC) and ventral (VL-PFC) areas. Advocates of this view have argued that the PFC is not organized by domain (e.g. spatial versus non-spatial), but by process, with ventral areas of the PFC supporting the passive storage and maintenance of items, while more dorsal areas are called upon when the task demands selection, monitoring, manipulation, or other 'mental work' to be performed on these items. This is the so-called 'maintenance' versus 'manipulation' processing distinction. While this view seems capable of explaining a wide range of findings, several studies have cast doubt on even the assumption that the VL-PFC contributes to storage in WM (e.g. Rushworth *et al*., 1997).

More recently, it has been argued that *all* of the PFC has an executive function in working memory, but that different subdivisions of the PFC perform this function at different levels of analysis (Ranganath, 2006). This emerging view asserts that the primary function of the PFC is to modulate the activity of other cortical areas where the items in memory are stored. Specifically, PFC representations enhance relevant information (or inhibit irrelevant information) represented in other parts of the cortex. When the information is specific to individual items in memory, more ventral PFC regions are engaged. When the information regards the integration of (or relations between) multiple items in memory, more dorsal PFC regions are engaged. Anterior regions of PFC, at the frontal pole, are implicated in coordinating and monitoring activity among different PFC regions to implement higher-order functions, such as planning. Accordingly, the primary role of the PFC is not in working memory, but in *working with memory* (Moscovitch, 1992; Moscovitch and Winocur, 1992).

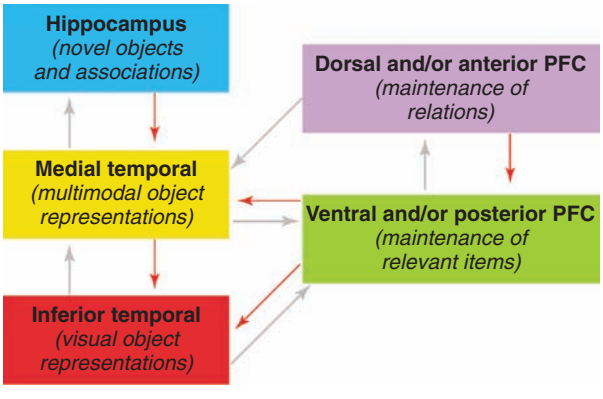
6.5 Combining prefrontal and MTL regions for working memory

Working memory is usually believed to operate over a few dozen seconds or minutes. However, even within a few minutes' time, we can find differences between different kinds of memory. In particular, you may have seen the word 'combining' only a minute or two ago, and yet you may not be able consciously to recall it. We can therefore make a prediction, based on our previous understanding of the role of MTL in explicit memory: if you can recall seeing the word 'combining' a brief time ago, your MTL should show activity in an fMRI experiment in which you are asked to recall the first word of this section. On the other hand, if you do not have an explicit memory of it – even over a short time period – your MTL should show less activity. But perhaps you will still retain a semantic memory of the title of this section, based on your neocortical encoding of that word.

We can therefore even describe working memory in terms of MTL, prefrontal cortex, sensory cortex, and the like. Figure 9.29 shows a model of how these brain



(a)



(b)

FIGURE 9.29 Combined brain regions work together for visual working memory. One view of visual working memory suggests that the hippocampus may encode WM items that are novel, the wider MTL may combine them with other modalities, and IT is involved in high-level visual object representation. The DL-PFCs and anterior PFC (purple) is involved with the short-term maintenance of relations, while the VL-PFC and posterior PFC is involved with maintenance of relevant items. As pointed out in the text, this is only one current hypothesis about the functions of these regions. However, it is widely believed that some network of functions like this may be needed to give a complete account of working memory. *Source*: Ranganath and D'Esposito, 2005.

areas may interact, based on a large number of studies of this kind (Ranganath and D'Esposito, 2005). Many of the specifics of this model are still debated, and we can expect new studies to cast some light on them. There seems to be an emerging consensus, however, that a complete explanation of working memory functions will require a multiregional model of this kind.

7.0 RETRIEVAL AND METACOGNITION

Clive Wearing knows that something is terribly wrong, but he has no idea what it is. 'I've just woken up for the first time. I'm conscious for the first time' is his only way to express it. For more than 20 years he has expressed the most intense frustration with his condition. Wearing must therefore have some *metacognitive* conception of his own cognitive functioning, unlike patient HM, for example, who is spared the emotional pain of sensing what he is missing. Metacognition is defined as the ability to know our own cognitive functions, and to be able to use that knowledge. Many neurological patients who are severely impaired have no metacognitive insight that anything is wrong (Milner and Rugg, 1992).

For retrieval to be effective, information at retrieval must overlap with the information that was learned or encoded. In addition, the person must have the goal of retrieving memories and paying attention to cues, as well as mentally searching for the desired memory. In all these processes, monitoring and verification are necessary, as is coordination of the various activities. Different regions of prefrontal cortex are implicated in many of these processes. The MTL is implicated most strongly with retrieval success for episodic memories. Automatic retrieval of a memory often occurs once the cue is found (Figure 9.30). Strategic or purposeful retrieval, however, is attention demanding and is impaired by any effortful competing task.

Metacognition is an important aspect of normal memory retrieval. A memory trace may be retrieved spontaneously, or more often by cues or reminders. A cue could be as simple as 'Recall the words you just studied' or as complex as 'Describe in detail what you did today'. The kind of self-monitoring we tend to do when we try to remember a missing word is a kind of metacognition that involves prefrontal cortex.

Schacter and colleagues (Schacter *et al.*, 1984) showed that memory for source in amnesic patients was related to the extent of their accompanying frontal deficits, rather than the severity of their amnesia.

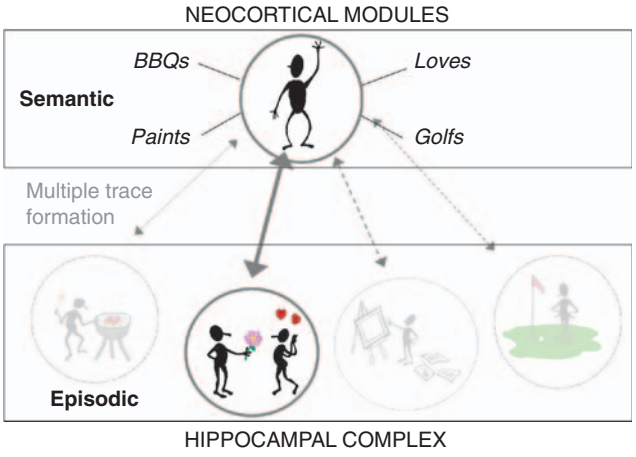


FIGURE 9.30 Retrieving semantic memories by using episodic cues and vice versa. We can often retrieve a semantic memory, like a fact about the world, by being cued with an episodic memory; the association can also go the other way. Thus episodic and semantic memory continue to be potentially connected, even if they exist relatively independently of each other in the hippocampal complex (MTL) and neocortex. Notice that most episodic memories for this semantic cluster of associations (on top) have faded. *Source*: Morris Moscovitch, personal communication.

Extending these findings to older adults, Glisky (Glisky *et al.*, 1995) showed that those with poor frontal function were impaired on tests of source memory but performed normally on tests of item memory, whereas the reverse was true of those with poor medial temporal function. Similarly, damage to prefrontal cortex leads to deficits in memory for frequency of occurrence (Smith and Milner, 1984) and temporal order (Milner, 1971; Shimamura, 1984) even when memory for the item itself is preserved.

The functional neuroimaging literature is consistent with the lesion literature. In comparison to tests of item memory, tests of source memory activate the DLPFC and the frontal pole more strongly (Fletcher and Henson, 2001; Fletcher *et al.*, 2005), as do tests of temporal order (Nyberg *et al.*, 1996; Cabeza *et al.*, 1997).

The role of metacognition, using prefrontal cortex, is especially dramatic when it fails. This is the case when people cannot recognize their own mistakes, as we see next.

7.1 False retrieval

There are deficits of retrieval that are quite remarkable. The case of confabulation is particularly important, the inability of some brain-damaged patients to tell that the 'memories' they are retrieving are entirely imaginary. One such case is illustrated in Box 9.5.

BOX 9.5 HW, a confabulating patient

HW is a 61-year-old man who was married to the same woman, Martha, for over 30 years and had four grown children, ranging in age from 22 to 32. He worked in a management position at a factory. He had an aneurysm of the anterior communicating artery, which feeds the medial frontal lobes and basal forebrain. Surgical clipping of the aneurysm was followed by widespread bilateral ischemia (loss of oxygen) and infarction. CAT scans confirmed widespread frontal damage, with sparing of the temporal lobes medially and laterally.

His brain damage led to memory problems exacerbated by confabulations and an unawareness of his memory deficits. His intelligence was normal, as measured by standard tests. HW's confabulations were spontaneous and, because he believed they were true memories, he attempted to act on them, making it difficult to let him live on his own. For example, there were times in the hospital that he believed he was at work, even though the hospital had beds, nurses, etc., and he wore hospital clothes. Many days at 5 pm he would prepare to go home and became frustrated and belligerent when he was told he had to stay.

Here is a part of an interview with HW:

Q: How long have you been married?
A: About 4 months.
Q: What's your wife's name?
A: Martha.
Q: How many children do you have?
A: Four. (He laughs). Not bad for four months.
Q: How old are your children?
A: The oldest is 32 . . . the youngest is 22. (He laughs again.)
Q: How did you get these children in four months?
A: They're adopted.
Q: Who adopted them?
A: Martha and I. . . .
Q: Does it all sound a little strange to you?
A: (He laughs) I think it is a little strange.
Q: Your record says that you've been married for over 30 years. Does that sound more reasonable to you?
A: No.
Q: Do you really believe that you have been married for four months?
A: Yes.

7.2 Hemispheric lateralization in retrieval

In light of the left hemisphere preference for language production (Chapter 11), it is perhaps unsurprising that memory functions may also be lateralized according to the nature of the material being processed. In working memory, for example, maintenance of verbal materials activates left regions in the parietal cortex and VL-PFC, whereas maintenance of non-verbal materials tends to be right-sided. Regions in the VL-PFC are also implicated in encoding information into long-term memory, and seem to interact with areas of the MTL in serving this function. Accordingly, both the VL-PFC and MTL have been found to exhibit hemispheric asymmetries in long-term memory encoding (Kelley *et al*., 1998).

Lateralization may depend upon the materials used (verbal, for example), and also upon the task and cognitive process. Endel Tulving and colleagues (Habib *et al*., 2003) proposed that, in general, learning is associated with greater involvement of the left PFC, while retrieval shows greater involvement of the right PFC (Figure 9.31). This model has received substantiation from a large number of neuroimaging studies.

Some researchers have questioned, however, whether this encoding/retrieval asymmetry may arise simply due to a greater dependence on verbal processes during learning than retrieval. The hemispheric bias seems to hold for episodic memories, while for semantic memory, both learning and retrieval seem more dependent on left hemisphere mechanisms.

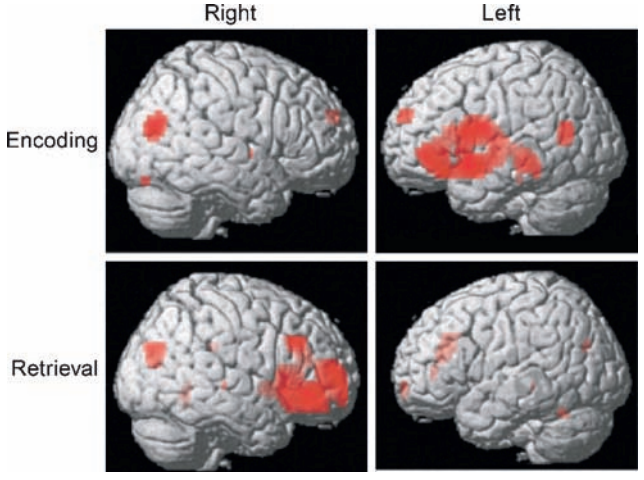


FIGURE 9.31 Left hemisphere for learning, right hemisphere for retrieval? Tulving and colleagues (Habib *et al*., 2003) found that the left hemisphere shows greater activity in episodic learning (encoding), while the right side showed more activity in episodic retrieval. *Source*: Habib *et al*., 2003.

A recent study by Rossi and colleagues (Rossi *et al*., 2006) using transcortical magnetic stimulation (TMS, see Chapter 4), a technique that allows temporary disruption to cortex in healthy subjects, supports the Tulving proposal. Their study showed that temporary disruption in the left PFC reduced learning efficiency, as measured by recognition accuracy. In contrast, TMS over the right PFC reduced retrieval efficiency. Thus, there seems to be a relationship between hemispheric lateralization and the learning-retrieval distinction.

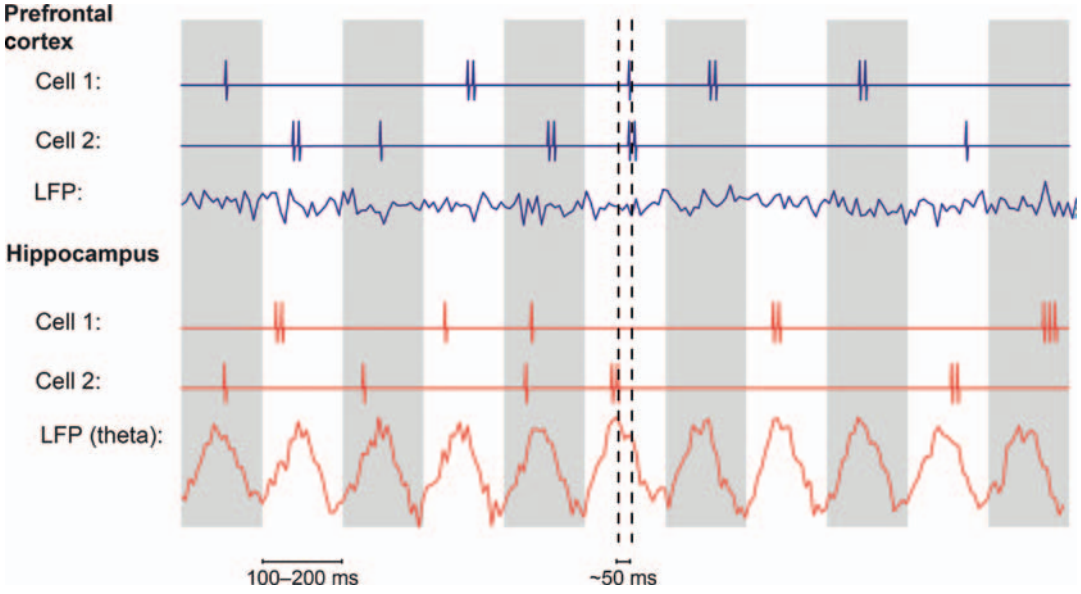


FIGURE 9.32 Theta oscillations may coordinate MTL and the prefrontal lobe during retrieval. Regular brain rhythms may serve to coordinate separate brain regions. Hippocampal theta is believed to reflect memory retrieval processes, and to coordinate prefrontal cortex with the MTL. *Source*: Jensen, 2005.

7.3 Theta rhythms may coordinate memory retrieval

A new literature shows that theta rhythms (5–8Hz) appear in the frontal lobes during memory retrieval. Depth electrodes placed in the hippocampi show that the MTL and prefrontal regions may be coordinated during retrieval (Siapas *et al*., 2005). Figure 9.32 summarizes these findings, which begin to show how the neural networks of prefrontal and hippocampal structures may cooperate to draw out and coordinate memory traces during retrieval.

8.0 OTHER KINDS OF LEARNING

We have only discussed some kinds of memory. We can only briefly mention some others, which make use of other brain structures (Figure 9.33). For example, the amygdala mediates fear conditioning (see Chapter 14). The cerebellum and basal ganglia are needed for habits and skills, as well as some kinds of conditioning. The thalamus is one of the great information hubs of the brain, constantly trading signals with cortex. It is therefore believed to be involved with cortical learning mechanisms.

Perceptual and motor learning involve the dynamic organization and reorganization of cortical maps (Chapters 2 and 5). This is called *neural plasticity*. For example, losing a finger will change the motor map representing the finger in the macaque cortex. In humans, brain surgery can alter sensory body maps very quickly, even during the operation. Life development itself can be viewed as a process of learning, adaptation, and memory formation (see Chapter 15). Finally, we now know that new neurons can be born throughout the lifetime, starting from stem cells (neural progenitor cells). The ongoing replacement of some neurons also involves a dynamic learning and adaptation process. There are many ways for the brain to learn. Though we have focused on more standard concepts of learning and memory, it is important to keep that in mind.

9.0 SUMMARY

The medial temporal lobes (MTL) are crucial to episodic memory in which we retain information about the conscious source of the memory. Amnesia patients with bilateral damage to the MTL are correspondingly unable to remember specific past episodes or to learn new ones. However, implicit learning and memory may be spared in these patients. Patients suffering from semantic deficits typically have damage

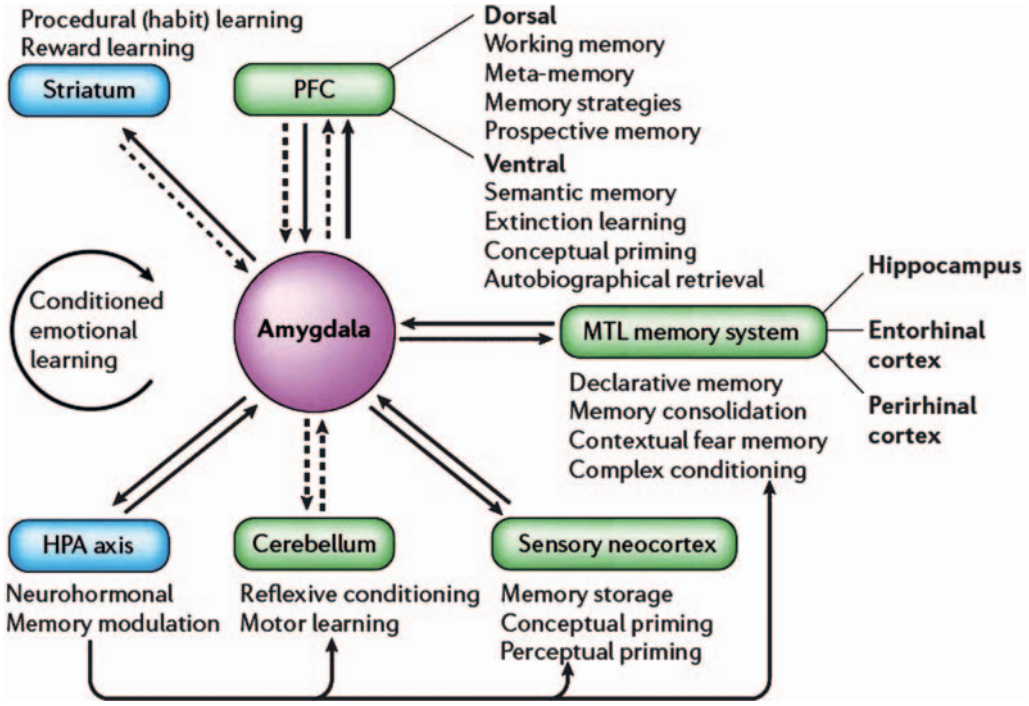


FIGURE 9.33 Different kinds of memory use different brain regions. An overview of multiple learning systems in the brain. The MTL system discussed in this chapter is involved in learning and recalling declarative, explicit memories; in memory consolidation; and the like. The PFC appears to be active in working memory tasks, metacognitive memory judgments, semantic memory, and conceptual priming. Perceptual priming involves sensory cortex, while motor learning and some kinds of classical conditioning seem to require the cerebellum. *Source*: Morris Moscovitch, with permission.

in the temporal lobe (especially the anterior and lateral parts) and prefrontal cortex. Such patients with semantic dementia, for example, may retain their episodic memory but are impaired on semantic tasks.

While explicit memory is assessed by accurate source memory reports, implicit methods like priming and sensorimotor performance may be needed to assess implicit memory types. Much of our learning is implicit, such as the learning of language. However, it is important to keep in mind that implicit learning requires conscious and attentive orienting to the stimuli to be learned. What is unconscious about implicit learning is not the original stimuli, but the inferential regularities that allow us to organize those stimuli. Sensorimotor skills are guided by the frontal cortex in collaboration with the basal ganglia and cerebellum. After overpracticing predictable tasks, such learned skills become less conscious and seem to rely only on subcortical structures like the basal ganglia.

Working memory can be decomposed into visual (the visuospatial sketchpad) and verbal (verbal rehearsal or the phonological loop). Further divisions are often possible, such as a separation between spatial and visual working memories.

A complete conception of human memory requires multiple brain regions: the MTL for explicit episodic memories; the prefrontal cortex for metacognition, maintenance, and use of memory; and sensory regions for perceptual and sensory memories. The cerebellum and basal ganglia are required for sensorimotor skill learning, in interaction with the frontal lobes. Further, sensory and motor halves of the cortex are in constant dialogue with each other, as when we hear ourselves speak. Finally, the amygdala is deeply involved in emotional learning, along with associated regions in the limbic system.

A wide range of memory deficits can be used to separate different memory components from each other. You should know some examples of such dissociations.

10.0 DRAWINGS AND STUDY QUESTIONS

1 Fill in the missing labels in the functional diagram given in Figure 9.34. Define each of the terms.

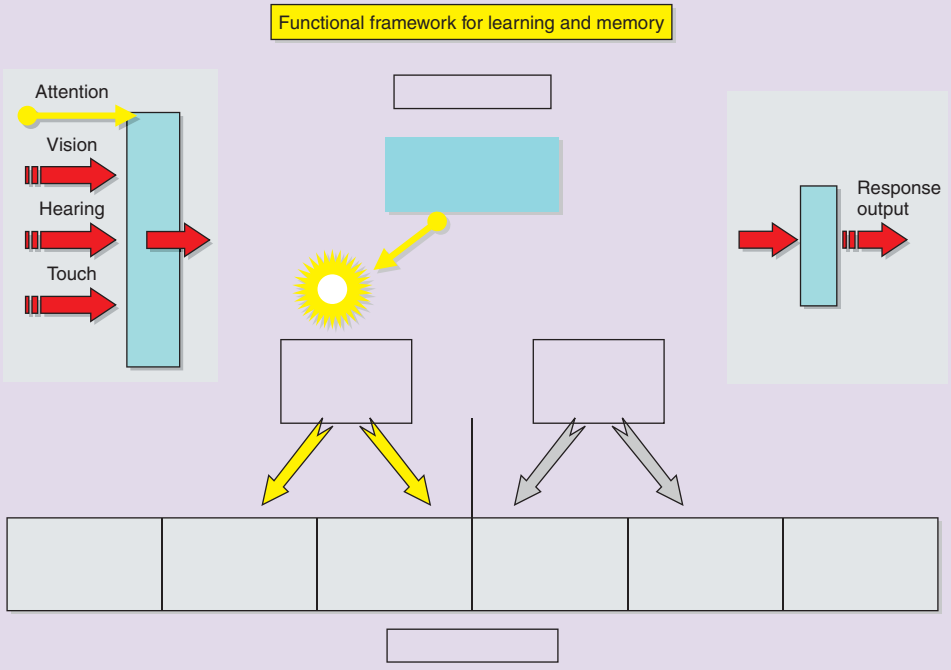


FIGURE 9.34 A functional diagram for learning and memory.

2 Label the regions and associated types of memory.

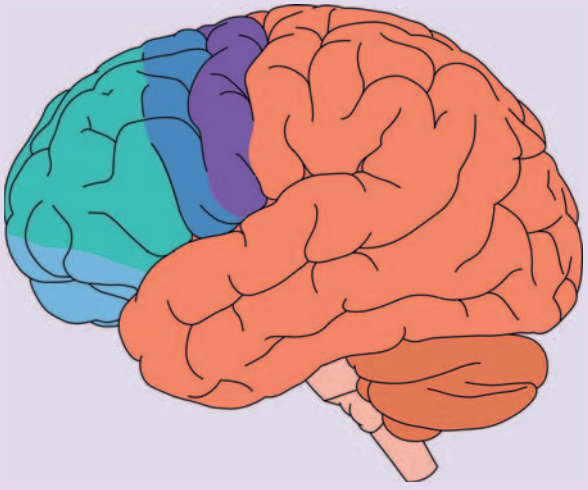


FIGURE 9.35 Relevant parts of the cortex.

3 Label the brain regions that are relevant to learning and memory in Figure 9.36.

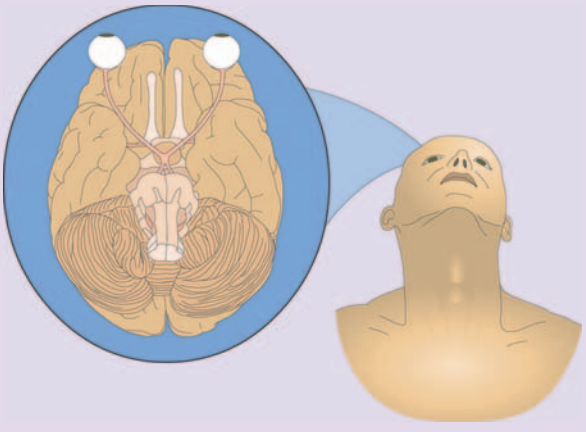


FIGURE 9.36 Location of some memory regions.

4 Label and describe:

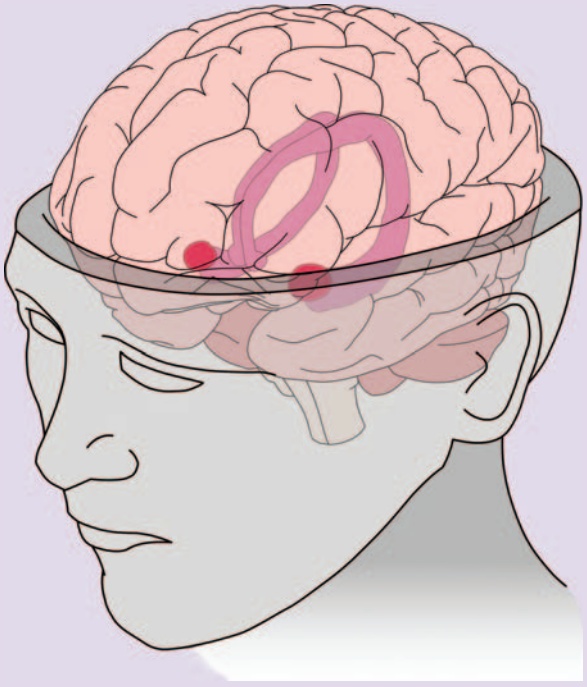


FIGURE 9.37 Location of some memory regions.

5 Label the abbreviations in Figure 9.38. What system does this describe?

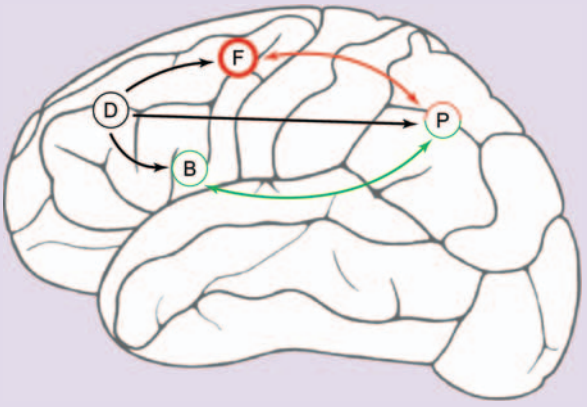
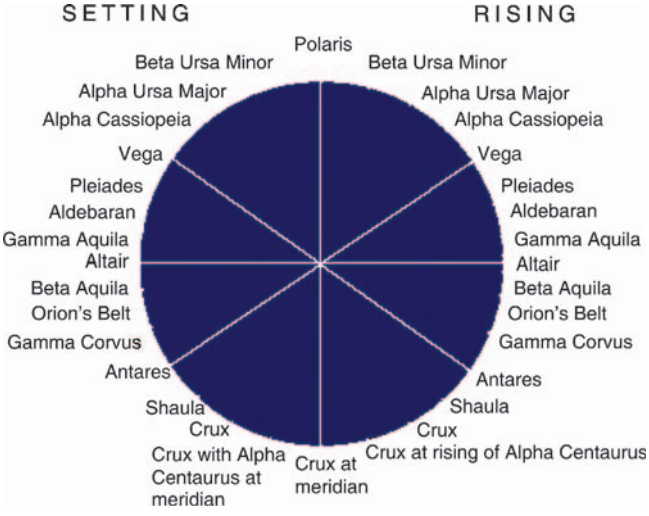


FIGURE 9.38 Brain areas theorized to be involved in specific aspects of memory processing.

Recruitment of executive attention is normally associated to a subjective feeling of mental effort.

Lionel Naccache, Stanislas Dehaene, Laurent Cohen,
Marie-Odile Habert, Elodie Guichart-Gomez,
Damien Galanaud, and Jean-Claude Willer (2004)



High level problem solving. Micronesian navigation is a highly complex and successful type of expertise. If it were not, island peoples of the Pacific Ocean could not navigate hundreds of miles in tiny craft to travel from island to island, surviving 'the stern test of landfall', as they have for thousands of years. The star compass on the upper right is an invention of oceanic navigators, who keep track of their location by noting the angle of rising and setting stars at night with respect to the North Star. High level knowledge of navigation was developed, memorized, and passed on by renowned experts. The outrigger sailing craft is a very efficient way to make the long journeys, but hardly without danger.

CHAPTER

10

Thinking and problem solving

OUTLINE

Human problem solving comes in two varieties, explicit and implicit. These two modes differ remarkably. Explicit thinking has clear, conscious goals and subgoals, and clearly defined steps for getting from a starting point to a solution. We can think of mental arithmetic as an everyday example. Explicit thinking involves greater executive control, higher mental workload, more frequent conscious access, and wider recruitment of cortical regions in pursuit of explicit goals.

In contrast, implicit problem solving may be more common, since we learn and practice many kinds of skills from early on in life. These problem solving skills become more proficient, implicit (unconscious), and automatic with practice. Understanding this sentence is an example, or completing a sentence that is predictable, so that we can tell what its last words are likely to be. Implicit problem solving takes less executive control than the explicit kind, less conscious access, less cognitive load, and less cortical involvement. It is much more dependent, on the other hand, on long-term memory and highly practiced routines. Very often, the unstated goal of learning is to turn explicit problem solving into the implicit kind.

In the realm of thinking, the historic debate between local and distributed brain functioning continues. With neuroimaging methods we can see far more local regions and processes than ever before. We might imagine therefore that localist theories might finally be winning the day, but that has not (yet) happened. While ever smaller and more specific brain regions are being examined, the evidence for widely distributed processes is still compelling (see Chapter 9). A number of theorists are therefore developing models that embody both localized *and* widely distributed neural networks.

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

FRONTIERS OF COGNITIVE NEUROSCIENCE

Focal attention and immediate memory

Every problem we try to solve in everyday life creates demands on our focal attention – what we are conscious of – as well as our immediate memory capacity. It also requires us to control to what we decide to pay attention. Nelson Cowan has spent a productive career studying these 'limited capacity features' of the human brain, along with their constant interactions with the large storehouse of long-term memory (Figures 10.1 and 10.2). Cowan writes that 'what appears to be a general capacity limit in working memory. . . is closely related to the contents of the conscious mind' (2008).

Focal attention is even more limited than psychologists have traditionally thought, according to Cowan's research. When careful experiments are done to exclude mental rehearsal and item grouping, the capacity of human focal attention comes down to four items or less. The traditional view was that immediate memory could hold 'seven plus or minus two' separate items, but that holds true only if subjects can rehearse the items to themselves. If subjects are asked to keep repeating 'the . . . the . . . the' to prevent them from rehearsing memory items, the capacity of immediate memory drops to four. The limit of four items has been associated with the posterior parietal cortex, but there is ongoing debate about the brain basis of limited capacity.

The 'magic number four' is quite stable across different kinds of items – digits, short words, simple sounds, visual objects, and so on. Cowan suggests that it applies to abstractions as well as perceptual events, images, and inner speech. To add two digits in memory we have to hold both of them for several seconds while calculating the sum. To understand a long sentence, we need to hold the first half in immediate memory in order to make sense of the second half. The sentence before this one is a good example. But there is evidence that each meaningful chunk of a long sentence is encoded into semantic units: Like the phrase, 'To understand a long sentence'. . . Humans are very skilled in semantic encoding, because we have a lot of practice in the job of understanding what people are trying to communicate to us. We tend to convert words into meanings as soon as we can do so.

FIGURE 10.1 Nelson Cowan, PhD, Department of Psychological Sciences, University of Missouri, Columbia, MO, USA.

The trick is therefore to make the best use of the limited capacity features we are born with. One approach is to *rehearse* a set of numbers to ourselves in inner speech. With rehearsal our working memory limit goes up to the traditional 'seven plus or minus two items'. But then we are using both our focal attention *plus* our immediate memory capacity for inner speech and mental rehearsal.

We can also lighten immediate memory load by scribbling a note or highlighting a sentence in a book. But writing is a recent human invention, not to mention audio and video recording. Before the invention of writing, humans were still able to solve complex problems, as we know from cultures that do not use writing. But they had to rely on their long-term memories (LTM), on mnemonics, and on highly elaborated knowledge of their world. A lot of cultures use speech patterns, like poetic rhymes, or alliteration, melodic chants, or poetic meter. That is how young children often learn their 'ABC's', through a song. It's not a bad way to learn brain anatomy either.

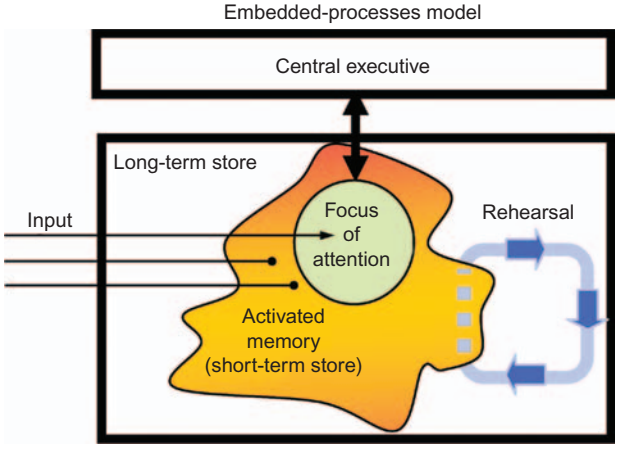


FIGURE 10.2 The cognitive psychologist Nelson Cowan suggests that immediate memory can be thought of as the activated parts of long-term stores. For example, repeating words to yourself activates existing vocabulary items in your long-term knowledge of language. *It is interesting that novel associations between known elements need to be brought together in the focus of attention in order to be encoded in long-term memory.* It is important to see immediate memory and the focus of attention, inner rehearsal, and other aspects of 'working memory' as *ever-present* aspects of normal cognition. Thus WM elements may be temporarily borrowed from LTM, and inner speech may simply utilize the 'outer speech' capacities of the human brain. *Source*: Nelson Cowan, personal communication.

Humans can solve problems with focal attention and immediate memory, as long as we combine them with our very large libraries of long-term memories. Every word you read may take up some limited focal attention, for just a moment, but the fact that you are thoroughly familiar with about 100,000 words and their meanings allows you to process rich 'word chunks', and not just meaningless blips and gurgles.

The part of long-term memory that is engaged with our present circumstances Cowan calls *active memory.* In reading this paragraph, your active memory is what you have built up in earlier chapters, along with all the active knowledge you are bringing to bear from sources. As authors, our effort is always to try to relate the scientific evidence to the knowledge that college students have at their mental fingertips.

Cowan points out that there are both time and capacity limits. Figure 10.2 suggests that what we are conscious of at any moment – the focus of attention–may be *capacity-limited*. In contrast, the 'active memory' in Figure 10.2 may be *time-limited;* it fades over time. As you focus on the sentence you are reading right now, for example, you will notice that it fades from memory in a few seconds.

Cowan suggests that the limited-capacity system may in fact run into *both* kinds of limits, depending upon the degree of attentional focus. If our mental focus zooms into an array of information, only a single item may become conscious; but if our mind's eye zooms out, up to four different items can be apprehended. We know that something like that is true for vision. Visual attention can zoom in and out of the details of the optical array, and we have seen how in the brain, the control of visual attention and eye movement involves the overlapping regions of the cortex (Chapter 8). Thus visual attention and eye movement control may have co-evolved over vertebrate evolution. A similar covert 'attentional zoom capacity' may have evolved along with the capacity to zoom into a physical light display. That is at least a testable hypothesis with the brain imaging tools we have today (Cowan, 2008).

Some questions are still debated. For example, Oberauer and Bialkova (2009) suggests that there is a conscious focus of attention that holds only one item, along with a 'fringe' that holds the three to five items. But there is no disagreement that the capacity numbers are very low.

The narrow bottlenecks in our mental information flow have a profound effects on learning and problem solving. People differ in their ability to guide and control their attention, to avoid distraction, and to persist in attending to a difficult task. Those differences correlate with individual cognitive traits, like standard intelligence, persistence, and processing reaction time. They also develop in predictable ways over the lifetime.

Halford, Cowan, and Andrews (2007) have proposed a specific relationship between working memory and reasoning, such as 'Knights and Knaves' puzzles (2007; http://en.wikipedia.org/wiki/Knights_and_Knaves). Knights and Knaves puzzles can be solved by binding elements (A and B) into slots (the knights and knaves).

Capacity limits in both working memory and reasoning can be attributed to the number of bindings to slots in a coordinate system or relation. Working memory is limited to approximately four items that can be kept active, whereas representations in reasoning are limited to four interrelated variables.

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2. Halford, G. S., Cowan, N., & Andrews, G. (2007). Separating cognitive capacity from knowledge: A new hypothesis. *Trends in Cognitive Sciences, 11*(6), 236–242.
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1.0 WORKING MEMORY

In a broad sense of the term, working memory is the domain of problem solving, language, and thought (Chapter 2). It is 'the set of mental processes holding limited information in a temporarily accessible state in service of cognition' (Cowan *et al*., 2005). We need working memory to perform mental arithmetic, to carry on a conversation, or to solve a pathfinding problem – How do I walk home from here? You cannot understand the sentence you are reading now without keeping words, ideas, and syntax in immediate memory. When we think about a problem, we constantly use inner speech and visuospatial thinking, directing attention to what is currently most important. As discussed in Chapter 8, attention leads us to become conscious of sensory events, of inner speech and action planning. Finally, whatever we are actively thinking about interacts with what we already know – our long-term store of memories, knowledge, and skills. Every word in this sentence is also part of our long-term vocabulary. Every eye movement you make is based on long-practiced routines (see Chapter 9). Thus, all the components of Figure 10.3 come into play in the realm of thinking and problem solving.

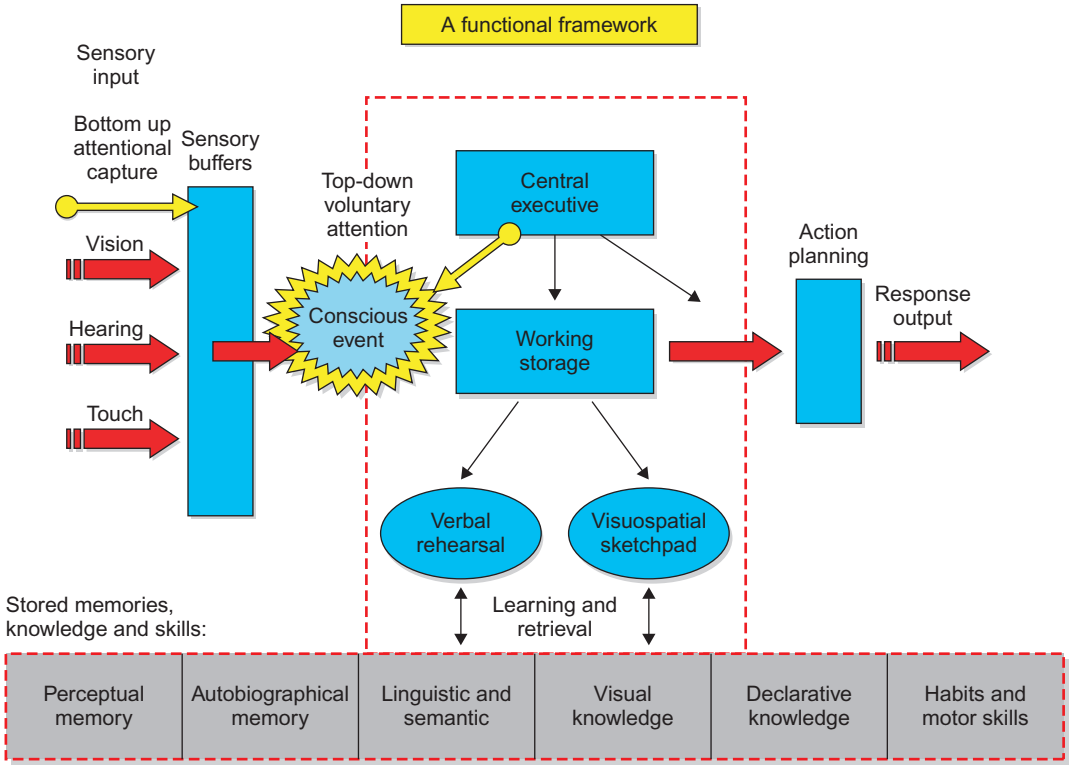

FIGURE 10.3 Problem solving in the functional diagram. Working memory (WM) is constantly involved in problem solving. However, WM functions also make use of stored information, such as the words and meanings of natural language, habits and motor skills, and various types of memory, shown in the gray boxes along the bottom of the diagram.

Surprisingly, much of this chapter is not about the colored boxes in the functional diagram, but about the row of gray boxes along the bottom. The colored boxes refer to active processes, the ones that require neuronal firing and integration. But they constantly run along habitual pathways encoded by previous active processes, which have now formed permanent networks of connections. Such permanent stores may not show up directly in brain imaging studies because they are encoded in the connective strengths between neurons. Methods like functional magnetic resonance imaging (fMRI) activity may therefore under-represent the vast amount of long-term knowledge.

1.1 Working memory overlaps with attention, conscious events, and episodic recall

Experiments generally aim to distinguish between working memory and related tasks. For example, in some working memory experiments, activity from single neurons in prefrontal cortex is recorded from cats or monkeys using a 'delayed match to sample' experiment in which the animal is given a stimulus, then must wait during a delay period after the stimulus disappears, and then point to the remembered stimulus among several others. Typical findings are that neurons keep firing during the delay portion, interpreted as an example of working memory function in which the animal must keep in mind the stimulus while waiting to perform a learned task (Goldman-Rakic, 1995; see Chapter 9). Selective attention presents people with two competing inputs. Conscious cognition compares conscious (reportable) to unconscious (unreportable) stimuli, using experimental methods like binocular rivalry (see Chapters 6 and 8). And episodic memory retrieval may involve asking people about their memory of yesterday's lunch. By using precise comparison conditions, we often find different parts of the brain 'lighting up'. New and reliable insights often come from these kinds of studies.

There is another side, shown in Figures 10.4 and 10.5, demonstrating widespread activation of frontal and parietal regions for four different brain activities that we often separate from each other: working memory, attention, episodic recall, and conscious perception. The overlap is enormous. That does not mean that they are identical theoretical constructs. They can be distinguished experimentally. But we cannot forget that the brain does whatever it does, not necessarily

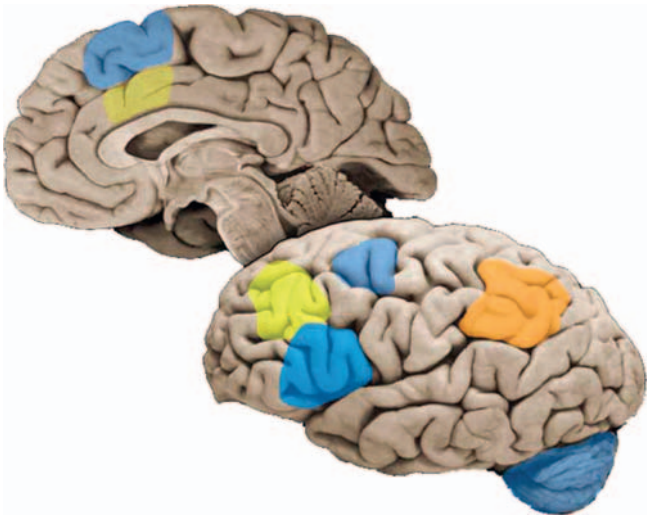

FIGURE 10.4 Proposed working memory regions. Common regions involved in working memory functions. *Source*: Schneider and Chein, 2003.

what we design our experiments to do. In this chapter, we will use the term 'working memory' to explore language and thought, but we might equally talk about it in terms of conscious and unconcious cognition, perception, and long-term memory. The most active aspects of working memory tasks are conscious or voluntary. It has been suggested therefore that passive working memory functions may be controlled by conscious/voluntary features, like perceptual input, recall, rehearsal, action planning, and response output (Baars and Franklin, 2003).

The limits of working memory must have posed difficult challenges for humans before the invention and spread of writing. Today we can scribble notes on a piece of paper, or look up information on the web. But over the neolithic period no one could write down their shopping list before going hunting and gathering. Perhaps for that reason, spoken language gives us many tricks and tools for chunking large amounts of information into smaller packages: sentences, words, phrases, sayings, narratives, personal names, and pronouns all serve as pointers and reminders (Figure 10.6). We also condense large amounts of knowledge by means of named abstractions and classification schemes (Box 10.1). Much of our large vocabulary consists of such labels. The vocabulary of natural language is a treasury of culturally compounded chunks of meaningful information (see Chapter 11).

Each chunk may point to a very large body of knowledge. In this book, the word 'brain' can be thought of as a link to everything you know about cognitive neuroscience. By pointing to knowledge via brief labels, we can optimize our cognitive bottlenecks.

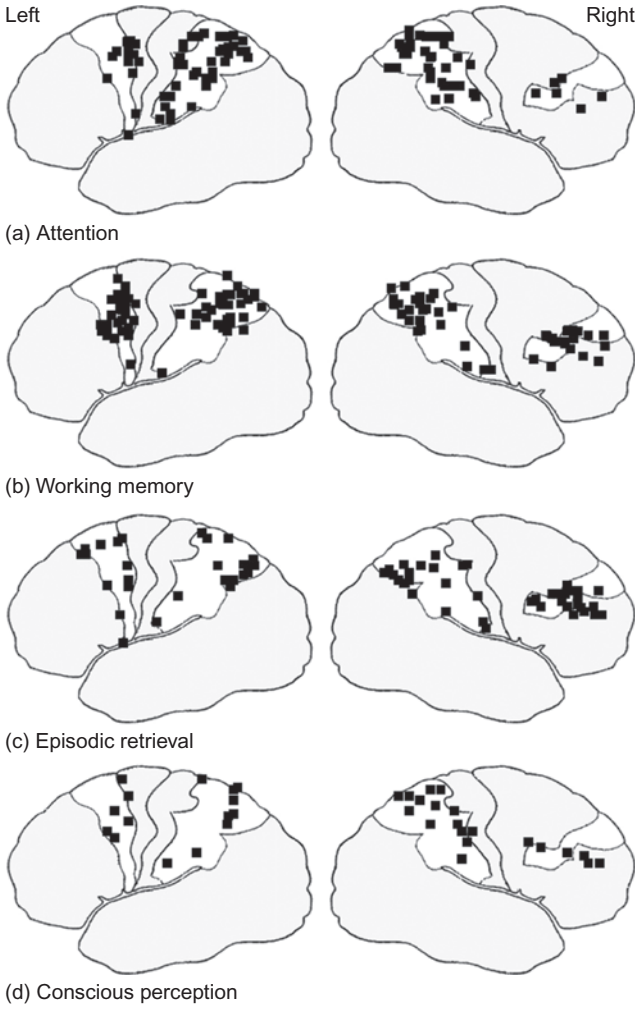

FIGURE 10.5 Overlapping brain regions support working memory, selective attention, autobiographical retrieval, and conscious perception. This figure shows schematically the widespread activation of frontal and parietal regions for four different brain activities that we often separate from each other: working memory, attention, episodic recall, and conscious perception. There is substantial overlap in these regions and it is not obvious that they can be separated. Attention = simultaneous selection, working memory = delayed selection, conscious perception = comparing a seen target to the same unconscious target, episodic retrieval = becoming conscious of an autobiographical event retrieved from memory. While these four brain activities are typically separately tested in experiments, there are many overlapping features of those functions. *Source*: Naghavi and Nyberg, 2005.

2.0 EXPLICIT PROBLEM SOLVING

Unterrainer and Owen (2006) described the basic conditions of explicit problem solving:

> First, one needs to create a mental representation of both the current situation and the goal. Furthermore, these representations have to be linked by establishing which actions are needed to transform the current state into the

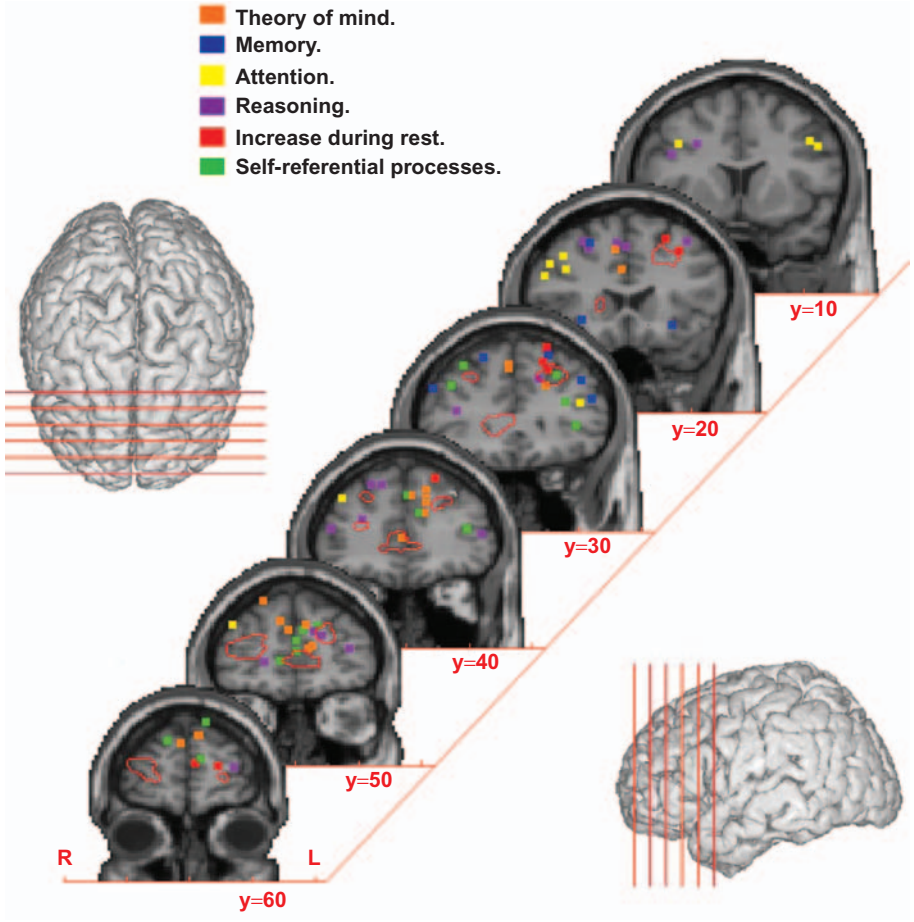

FIGURE 10.6 Some frontal capacities for high-level thinking. The frontal lobes are also needed for advanced skills, ranging from the ability to understand other people's intentions to reasoning, imagination, and self-understanding. These frontal capacities constantly interact with posterior and subcortical brain regions. *Source*: Wicker *et al.*, 2003.

goal state. Problems therefore have three general characteristics: (1) an initial state, or the state in which the problem solver sorts out the givens; (2) a goal state, or the solution state that the problem solver tries to achieve; and (3) the steps that the problem solver takes to transform the initial state into the goal state that initially may not be obvious (Sternberg and Ben-Zeev, 2001).

Problem-solving can be thought of as finding a path through a maze of *choice-points* between possible *subgoals* toward a final goal. In the standard puzzle called the Towers of Hanoi, we are given a problem as in Figure 10.8. The goal is to end up with the three disks on the rightmost rod in the same order they are shown at the beginning. This requires subgoal planning. The tree of choices is called a *problem space*, as in Figure 10.9. Some sequences of steps lead to a solution while the others do not. Figure 10.10 shows brain regions active while solving Tower of Hanoi puzzles, notably the dorsolateral prefrontal cortex (DL-PFC).

Towers problems are puzzles rather than real-life problems. Real problems for human beings are such things as how to travel from one place to another across difficult and dangerous territory, how to find food and shelter, how to protect children and group members from dangers, how to maintain relationships, or how to prevail in a competitive situation. Life problems are rarely easily defined, and the stakes can be much higher. Nevertheless, even simple puzzles can represent important features of real problems. Ideas like goals and subgoals, choice points in a problem space, and costs and benefits show up in many kinds of ways. While a complete problem space description is rarely available for more real-life problems, a useful strategy is to break down larger problem spaces into subgoals that can be described explicitly and completely.

2.1 Executive control in problem solving

The cliché that 'generals tend to wage the previous war' applies to many kinds of problems. In science, for example, there is a tendency, even among the most celebrated scientists, to become focused on one major approach which may not always work. One famous case is Albert Einstein, who had an intense

BOX 10.1 How chess experts chunk known game positions

Expert memory for chess position

Much of what is known about expertise goes back to De Groot (1946)[a] and Chase and Simon (1973)[b]. One of De Groot's enduring contributions was to demonstrate the existence of clear differences between levels of player in a memory task, involving the brief presentation of a position taken from a tournament game. Typically, players at and above master levels recall the entire position almost perfectly, but weaker players perform poorly (see Figure 10.7).

However, Chase and Simon found no difference in recall of *random* positions between their three subjects: a master, a class A player, and a novice using their model CHREST (Chunk Hierarchy and REtrieval STructures). This uniformly poor recall of random positions taken together with the superior performance of masters and grandmasters on game positions presented such a vivid illustration of the principle that knowledge is the key to expertise that it has become a classic finding, widely cited in textbooks of cognitive psychology and in papers on expertise.

However, an earlier version of CHREST, a re-implementation and extension of MAPP (Memory-Aided Pattern Recognizer, Simon and Gilmartin, 1973)[c], made contrary predictions about the recall of random positions. In the chess simulations, CHREST is trained from a database of master games, identifying patterns of pieces in these positions. As expected, the model's ability to remember game positions improved as the number and average size of its chunks increased. However, the model also showed a small, but robust increase in recall with random positions. The skill differences in recall were the result of an easily explained mechanism: simply by chance, a larger discrimination network is likely to include patterns found in random positions. A systematic review of experiments that asked chess players to recall random positions[d] yields 12 studies in which masters demonstrated some superiority, and only one, Chase and Simon's study[b], where the master actually did worse than novices. Although the skill differences were not significant in most studies because of lack of statistical power, the effect becomes clear when the various studies are pooled (see Figure 10.7(b)). The fact that perceptual chunking provides masters with an advantage even in random positions offers strong support for chunk-based theories, and is hard to explain for theories of expertise based upon high-level knowledge or schemata[a]. For a review, see Gobet, 1998.

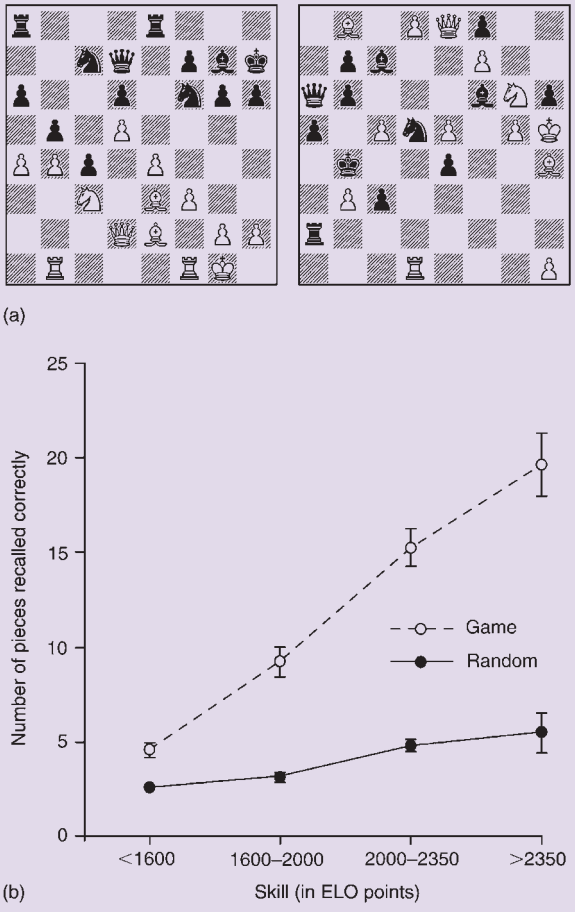

FIGURE 10.7 (a) Types of positions typically used in chess memory research. A game position taken from a masters' game (left), and a random position obtained by shuffling the piece locations of a game position (right). (b) Mean number (averaged over 13 studies) of pieces placed correctly as a function of position type (game or random) and skill level. Positions had 25 pieces on average, and the presentation time was ≤10 s. Error bars indicate standard errors of the means. *Source*: Adapted from Gomet and Simon, 1966.

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dislike of quantum mechanics, even though it made it possible to explain phenomena that could not be addressed any other way. Einstein was philosophically deeply opposed to the idea that physics could be statistical rather than deterministic, and tried for 30 years to find an alternative to quantum theory. Hundreds of other examples can be found in the history of science. 'Fixedness' appears to be a very widespread difficulty in human problem solving.

It is easy to induce *functional fixedness* in problem solving (Duncker, 1945). One only needs to encourage subjects to become accustomed to one way of reaching

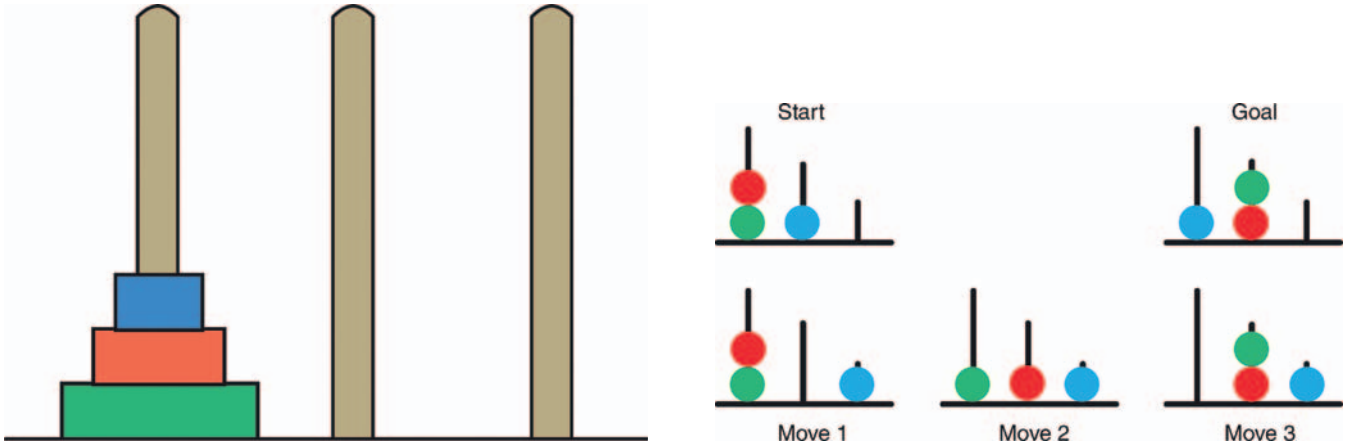


FIGURE 10.8 The Towers of Hanoi. Shallice (1982) used the puzzle called the Towers of London (also called Towers of Hanoi) to diagnose frontal impairments. The task is to move the rings one at a time to match a target scheme. The difficulty level of these puzzles can be adjusted, as in the figure on the right side. Tower problems have been standardized for clinical testing, and have led to a great deal of research. Instructions on effective strategies improve performance for people with intact frontal lobe functioning. *Source*: Miller and Wallis, in Squire *et al*., 2003.

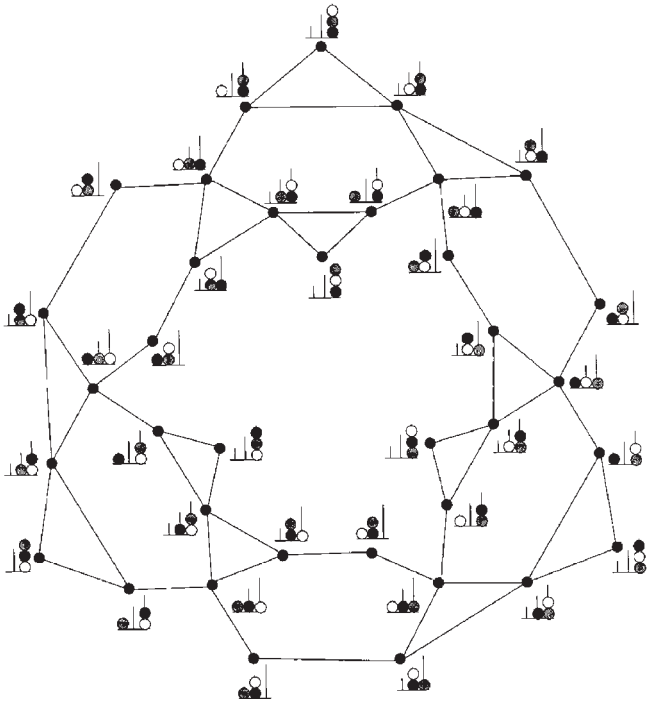


FIGURE 10.9 A problem space. The problem space for the towers puzzle shows many possible positions, choice-points, and pathways.

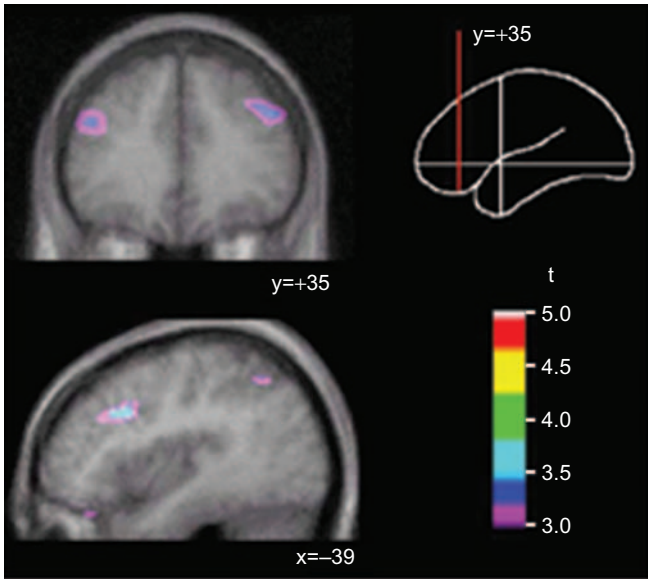


FIGURE 10.10 Dorsolateral prefrontal cortex in tower problems. Tower problems elicit brain activity in the middle part of the dorsolateral prefrontal cortex (DL-PFC), a crucial region for executive functions. *Source*: Unterrainer and Owen, 2006.

the goal, even when that way no longer works. Functional fixedness can be shown in a great range of tasks. In language there are 'garden-path sentences' that mislead readers into misunderstanding the syntax of a sentence. A famous example is the sentence, 'The horse raced past the barn fell'. This grammatically correct sentence can cause many minutes of puzzlement. The problem comes from the fact that there is an outer clause, 'The horse ... fell' and an inner clause, 'raced past the barn'. The sentence can be rephrased as, 'The horse *which* raced past the barn fell'. However, in English the marker 'which' is optional for subordinate clauses.

The sentence therefore leads the reader down the wrong path, and we only discover at the end of the sentence that we are left with an extra verb, 'fell'. Such misleading sentences are far more common than we realize, simply because we normally interpret language based on contextual knowledge. For example,

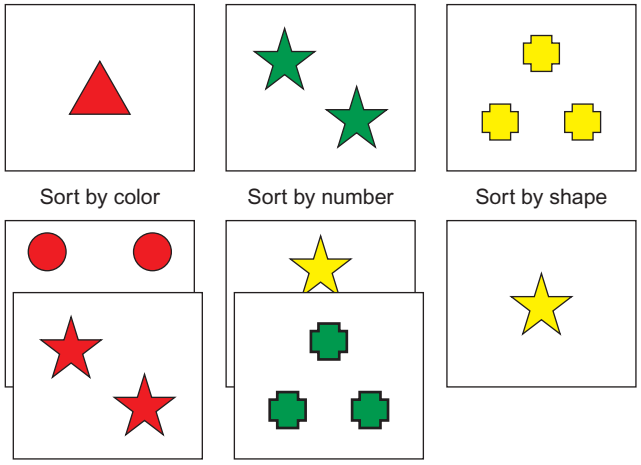


FIGURE 10.11 The Wisconsin Card Sorting Task. The WCST encourages subjects to adopt a certain rule like 'the yellow color predicts correct cards'. At some point a different rule comes into play, such as *number* or *shape* of items. This is a challenge to our ability to think of alternatives to the first rule, and people with frontal lobe impairments will typically perform poorly when the rule is shifted. *Source*: Grant, 1993.

we might be watching horses racing around a stud farm, and know that one horse raced past the barn, while another one raced past the farmhouse.

Fixed and misleading mental sets are very common. Figure 10.11 shows the Wisconsin Card Sorting Task (WCST), which is designed to induce a misleading set in a simple card sorting task. Subjects are asked to guess which card is 'correct', using color, number, or shape. They are given feedback for each guess. Initially they are rewarded for one pattern, e.g. the rule that the color yellow is always correct. At some point the rule is changed without telling the subjects. The time and number of missed trials needed for subjects to shift set is taken as an index of their ability to test different hypotheses.

Patients with impaired frontal lobes often lack cognitive flexibility, and tend to score low on the WCST. *Perseveration* in unsuccessful strategies is a marker of disorders like Alzheimer's dementia (Ridderinkhof *et al*., 2002). The WCST is especially useful when frontal lobe damage is too subtle to be detected by standard brain scans.

Changing rules is difficult when we are mentally fatigued or drowsy or otherwise impaired. Even switching from one task to another seems to require additional mental resources beyond those involved in routine and automatic actions (Figure 10.12). Thus, drivers who are sleepy might find it harder to make fast decisions in unpredictable traffic situations, presumably because their frontal lobe may be functioning below par. Workers

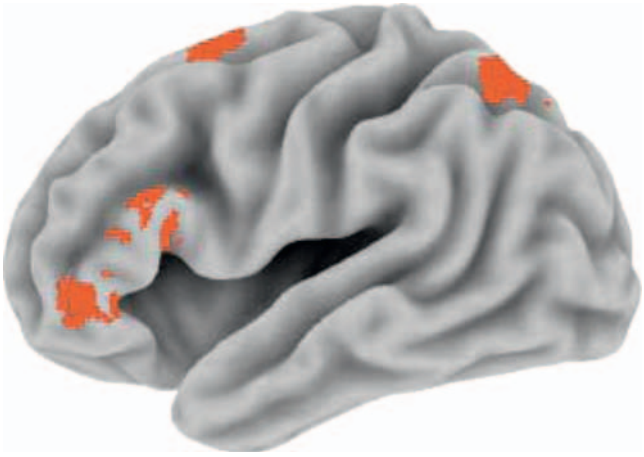


FIGURE 10.12 Task switching. Regions of high activity during task switching overlap with brain areas required in other executive tasks. Compare to Figure 10.19. (page 59). *Source*: Braver *et al*., 2003.

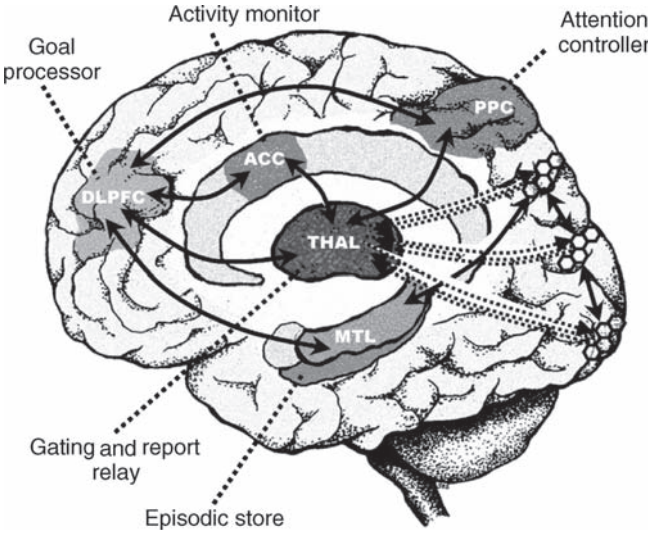


FIGURE 10.13 A proposed model. On the outer surface of each hemisphere, peak activity during problem solving appears in the dorsolateral prefrontal cortex (DL-PFC). During task conflict or errors we find high activity in the forward part of the cingulate cortex (ACC). These two territories consistently show high activity when a cognitive task is difficult. *Source*: Schneider and Chein, 2003.

on night shifts have been shown to be more error prone than daytime workers, and frontal lobe function may have something to do with that difference as well.

Figure 10.13 shows a model of executive functioning from Schneider and Chein (2003). We will use it to summarize our current knowledge about explicit problem solving. The area marked DL-PFC (dorsolateral prefrontal cortex) is considered to be a goal processor. Thus, in the Towers of Hanoi, goals and subgoals would be represented in this region. The ACC (anterior cingulate cortex) monitors errors and conflicts

between goals (see Chapters 8, 11, and 12). PPC (the posterior parietal cortex) is involved in attentional control (see Chapter 8), while the medial temporal cortex (MTL) is the gateway to episodic memory, the autobiographical store of past conscious experiences (Chapter 9). Finally, the thalamus (marked THAL) is considered to be a 'gating and reporting relay'. The last label may be controversial, and really stands for a broader thalamo-cortical gating and reporting system (see Chapters 5 and 8).

We have already seen the DL-PFC involved in the Towers of Hanoi problem and in task shifting (above). Figure 10.14 shows how both the DL-PFC and ACC become involved in five different tasks requiring executive effort, including response conflict (as in the Stroop task), novelty, immediate memory loading, and even perceptual difficulty.

Figure 10.15 summarizes ACC activation across yet different executive tasks, including emotionally demanding ones. As we might expect, executive regions become involved in a very wide range of conditions that require flexible decision making. In contrast, as we will see, unconscious memory traces and skills do *not* recruit these executive regions. Instead, they are thought to be encoded in widespread traces in the temporal cortex and elsewhere in the brain (Moscovitch *et al.*, 2006).

This model therefore shows general-purpose functions, like:

1. sustained goal pursuit and deciding on subgoals
2. maintaining attentional focus on the task
3. inhibitory control over distracting thoughts and emotions
4. metacognitive monitoring of the quality of required sensory, motor, language, and immediate memory functions.

We will later see how executive processes also make constant use of stored information, including chunked information that is needed to circumvent capacity limits.

3.0 MENTAL WORKLOAD AND CORTICAL ACTIVITY

Effortful tasks show a wider spread of brain activity, even beyond the executive regions of the frontal cortex. For example, in a classic study, Smith and Jonides (1998) found dramatically expanded cortical activity

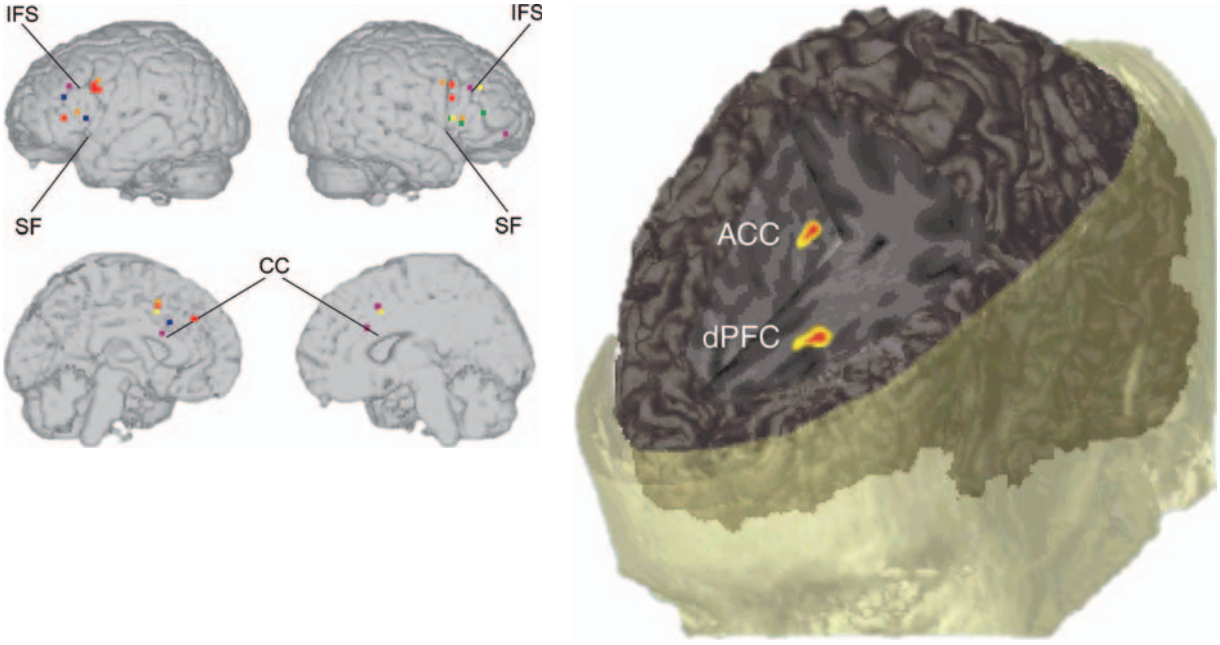


FIGURE 10.14 Mental effort activates executive regions. Left panel: Duncan and Owen (2000) showed that five very different tasks that all involve mental effort activate lateral and medial sides of the frontal lobe. The five tasks shown are response conflict (green dots), task novelty (pink), the number of elements in working memory (yellow), the delay required in working memory (red), and perceptual difficulty, such as visually obscured stimuli (blue). Abbreviations: CC: corpus callosum; IFS, inferior frontal sulcus; SF: Sylvian fissure. The image on the right shows a different perspective of the ACC (anterior cingulate cortex) and DL-PFC (dorsolateral prefrontal cortex) (MacLeod and MacDonald, 2003). *Source*: *Left*: Duncan and Owen, 2000; *right*: MacLeod and MacDonald, 2003.

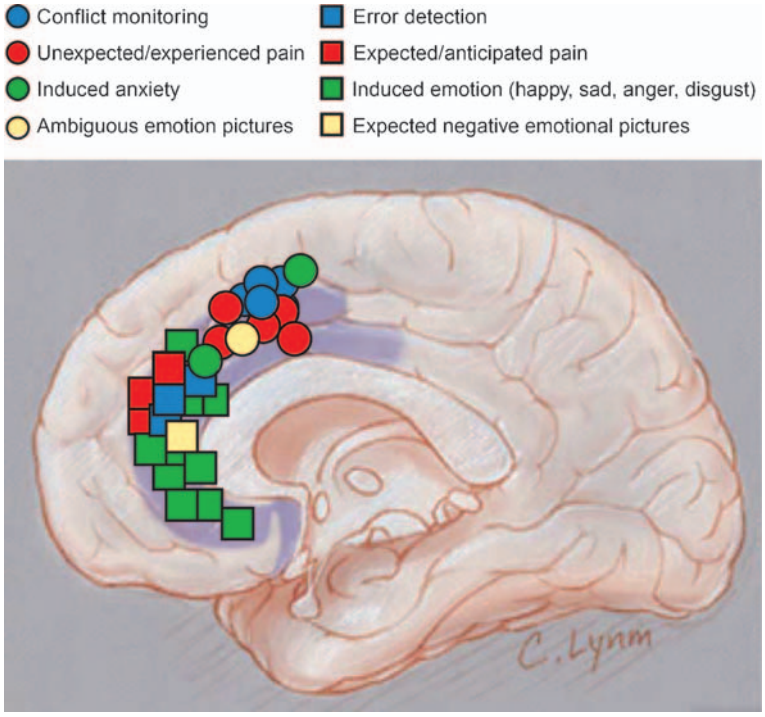


FIGURE 10.15 Error detection and resolution. As in Figure 10.12, this one shows a number of different tasks, all of which activate parts of the anterior cingulate cortex (ACC). Previous studies showed that conflict monitoring (as in the Stroop effect) evoked ACC activity. However, tasks as different as ambiguous emotion picture; induced anxiety; expected, unexpected, and experienced pain; induced emotion; and expected negative emotional pictures, all showed reliable ACC activation. Other studies locate the emotional aspects of ACC activation to the anterior tip of the ACC, and cognitive activation, as in error detection, to the upper part of the ACC. *Source*: Botvinick *et al*., 2004.

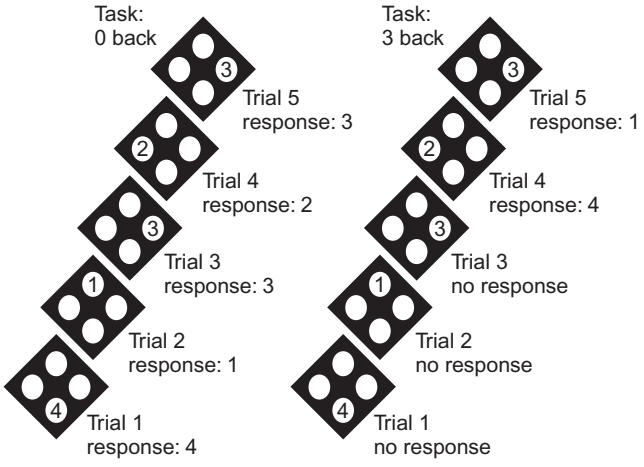


FIGURE 10.16 Loading working memory: the n-back task. In the 0-back case, subjects only need to report what they see. As n goes from 0-back to 3-back, they must keep in mind more items, keep track of the order of each one, and at the same time notice each new slide to add to their mental stack. Task difficulty rises steeply with the number of items to be kept in running memory.

as a function of memory load. These authors used an 'n-back' technique (Figure 10.16). Subjects were shown a series of memory items. In the 1-back condition, they only had to recall the last item; in the 2-back case, the item shown before the last one; in the 3-back case, the item shown 3 slides before. The n-back task is the human equivalent of a hamster's running wheel. One must keep constantly working to keep up with the flow of information. Difficulty level rises very quickly with the number of items to be kept in mind. Results from the Smith and Jonides (1998) study are presented in Figure 10.17.

What we cannot see yet, even with advanced brain recording methods, is the strength of connections between brain cells. Figure 10.18 indicates that mental effort also changes connection strengths, the neural signaling density between cortical locations.

Judging by brain activity, cognitive effort is one of the biggest factors in brain functioning. That may seem odd. After all, tasks that take mental effort are not usually the most complex or sophisticated ones we perform. The sentence you are reading right now is far more complex than the n-back memory task we just discussed. Why doesn't the sophisticated language processing use a great deal of brain activity? Figure 10.19 suggests an answer: the level of activity in cortex (at least) drops with practice and automaticity. While language analysis is extremely complex, it is also highly practiced over a period of years. Thus, neural firing or brain metabolism is not a direct measure of the complexity of some mental process. Rather, it seems to indicate the recruitment of neuronal resources that are needed to work together to perform a task that is new or unpredictable. Once even very complex processes are learned, they seem to require less cortical activity. Automaticity also involves a loss

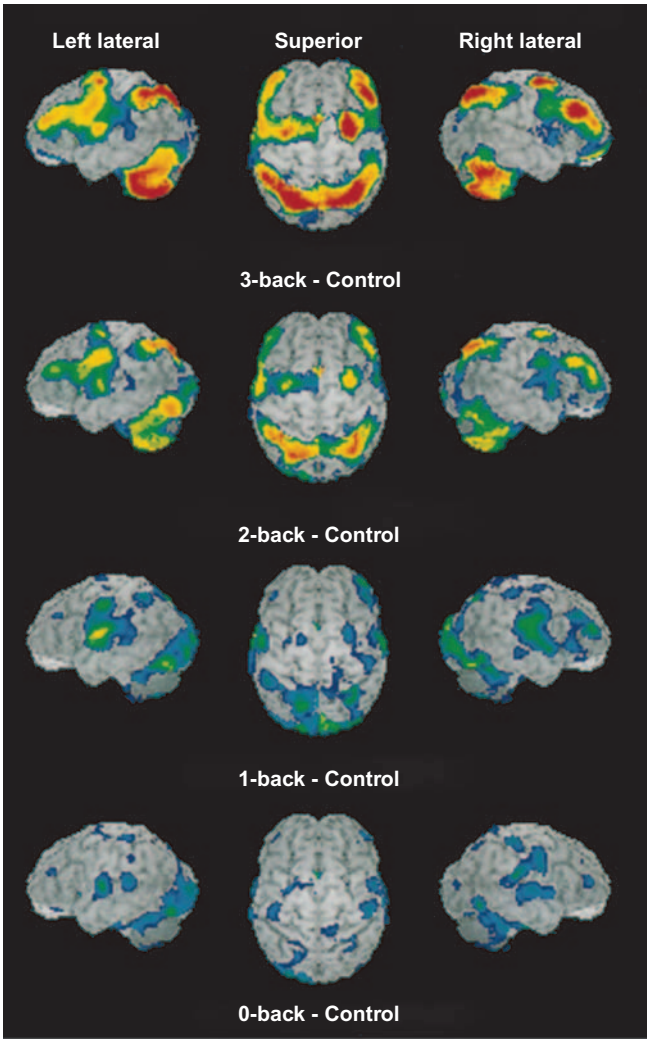


FIGURE 10.17 Effortful tasks recruit wider brain regions compared to a no-memory control. Notice that increased working memory load recruits progressively wider regions, including parts of frontal and posterior cortex and cerebellum. Thalamus and basal ganglia are not shown, but are likely to be more mobilized as well. *Source*: Smith and Jonides, 1997, Figure 10.

of conscious access and voluntary control, as assessed by behavioral measures (Schneider, 1995; Baars, 2002).

4.0 USING EXISTING KNOWLEDGE

One theme of this chapter is how the human brain makes constant use of chunking strategies to solve problems within the capacity limits of immediate memory. How does the brain manage this?

One way to think about chunking is to reverse our usual concept of working memory and emphasize the degree to which mental operations make use of existing learning, encoded in forests of acquired synaptic connections (see Chapter 3). Working memory is crucially dependent upon stored long-term information. Your understanding of this sentence depends upon your memory for words, sentence structure, and meaning. Cowan (2001) and others therefore suggest that we can flip the roles of working and long-term memory, and conceive of working memory as playing upon years of previous stored information (Figure 10.2).

Current brain imaging methods reveal active neuronal signaling, but not the synaptic connectivities that encode those years of learning. Brain recording is therefore much like watching the flow of traffic in a city from outer space. We might easily see car lights streaming back and forth each day. But with our current instruments it is harder to observe the slower process of building new roads, highways, and parking lots that make it possible for traffic to move. Yet the entire system depends upon the physical layout of streets and highways, a kind of permanent memory of the city. A space observer could learn a lot from traffic patterns – one neighborhood may be a financial center, another one might have an airport. But, on weekends,

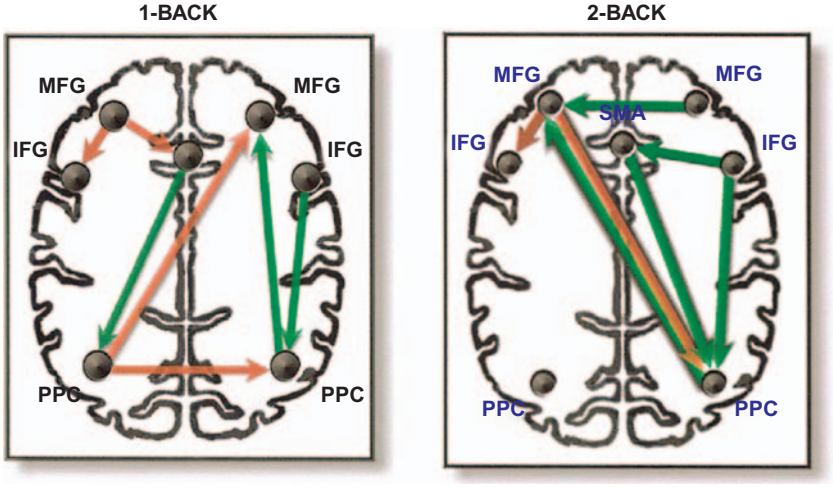


FIGURE 10.18 Connection strengths change with task difficulty. The colored lines in the two brain diagrams indicate connection strengths between executive and other regions of the brain. Connection patterns change with increase in memory workload. *Source*: Honey *et al.*, 2002.

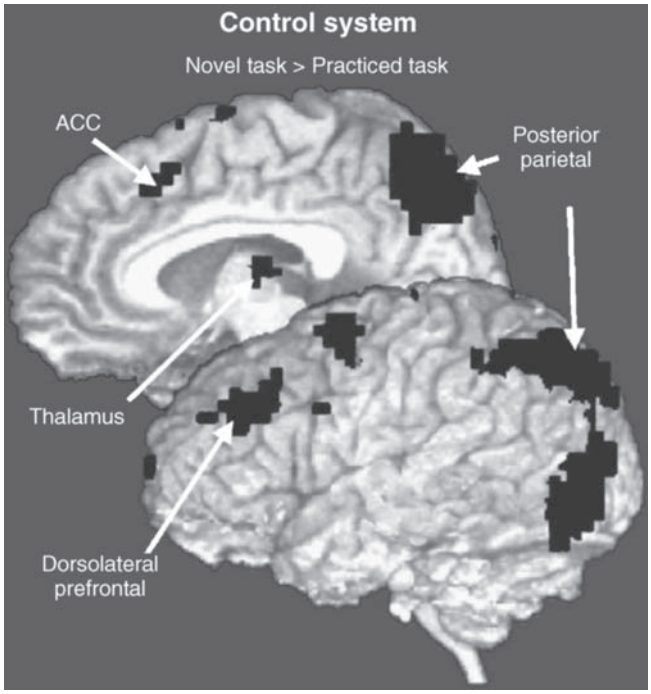


FIGURE 10.19 Executive activity drops with practice. After practice in predictable tasks, cortical activity is dramatically reduced. This summary image shows reductions in executive regions (compare to Figure 10.12). However, other active cortical regions also show decrements with increased practice and automaticity. It is believed that control over routine tasks is relegated to subcortical regions like the basal ganglia and cerebellum. However, intermittent cortical control may remain at unpredictable choice-points in the task. *Source*: Schneider and Chein, 2003.

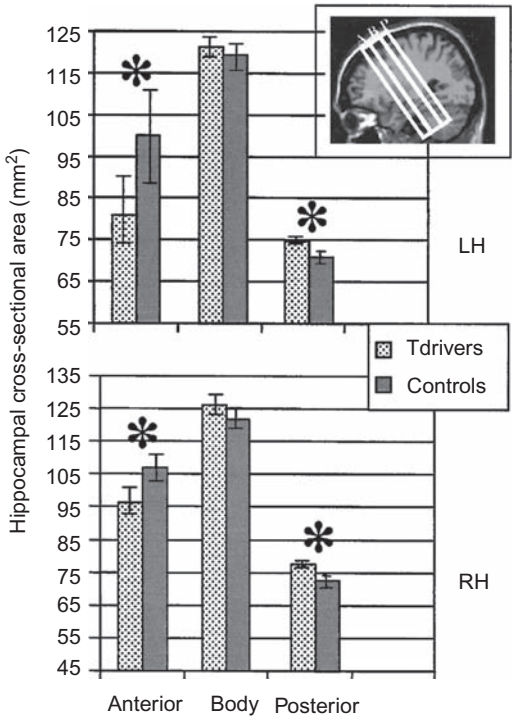


FIGURE 10.20 Long-term brain changes in experts. Maguire *et al*. (2000) found that London taxi drivers showed larger posterior hippocampal volume on the right side than controls, consistent with the known role of hippocampus in spatial processing. However, this methodology does not prove that the number of synaptic connections is greater as a result of expertise. The difference could be due to other factors, such as myelination, the number of support cells, and the size of neurons. However, the sheer size of relevant brain regions seems to relate to expertise in other studies as well. *Source*: Maguire *et al*., 2000.

traffic flows might change. In bad weather more people may stay home. Depending upon unknown conditions traffic may flow along different routes, while still making use of the permanent connectivity of streets and highways. Just watching signal flow reveals only part of what makes the brain work.

Thus, knowing the connections and their strengths – the streets and highways – is an essential part of the puzzle that is still hard to study. Yet we know that long-term memory is crucial (look back at Box 10.1). We will take a look at evidence for long-term changes next.

4.1 Practice and training may change connectivities in the brain

As discussed previously, long-term memories are believed to be encoded in the connections between neurons. If memories are encoded in synaptic connections, they may not show up directly in brain measures like fMRI. Connections and active brain processes are not necessarily correlated; in fact, in the section above, we found evidence that more skilled and expert tasks might show less cortical activity. Thus, long-term stores may not be reflected in fMRI, magnetoencephalography (MEG), electroencephalography (EEG), and other standard measures.

Other measures are currently being developed to assess the efficiency of synaptic connections in the brain's neural networks. One possibility is shown in Figure 10.20, from a classic study by Maguire *et al*. (2000) on London taxi drivers, who must pass examinations about their knowledge of the complex street map of London. After years of experience in a real-world spatial task like this, would their brains show differences as a result?

4.2 Semantic memory

We have previously noticed the close connection between sensory and motor systems in the brain, and their use for endogenous or 'inner' cognitive functions.

It seems that visual imagery makes use of visual cortex, and that inner speech makes use of speech cortex. Figure 10.20 may take that rule of thumb a step farther, in that semantic concepts seem associated with the temporal lobe (including the medial temporal region and the hippocampal neighborhood, not visible in the figure). More generic concepts are believed to be encoded posterior to unique concepts in the left lateral temporal lobe. Biological motion – the rather sinuous movements of animals – is located near area MT (the visual motion region), while human-made artifacts and instruments seem to activate a slightly different part of the occipital-temporal area. There is independent evidence that tools may also activate regions close to somatosensory and motor cortex. Hauk *et al*. (2004) recently found fMRI evidence that, 'action words referring to face, arm, or leg actions (e.g. to lick, pick, or kick) . . . differentially activated areas along the motor strip that either were directly adjacent to or overlapped with areas activated by actual movement of the tongue, fingers, or feet'. This supports the general theme of sophisticated and biologically recent semantic capacities making use of long-established brain regions adapted to dealing with the sensorimotor world.

In a recent review, Martin and Chao (2001) wrote:

> Distributed networks of discrete cortical regions are active during object processing. The distribution of these regions varies as a function of semantic category. The same regions are active, at least in part, when objects from a category are recognized, named, imagined, and when reading and answering questions about them.…
>
> Taken together, these data suggest that ventral occipitotemporal cortex may be best viewed not as a mosaic of discrete category-specific areas, but rather as a lumpy feature-space, representing stored information about features of object form shared by members of a category. . . .
>
> A feature-based model can accommodate the observation that an arbitrary category such as chairs elicited a pattern of neural activity distinct from other object categories (i.e. faces and houses). Clearly, it would be difficult, as well as unwise, to argue that there is a 'chair area' in the brain. There are simply too many categories, and too little neural space to accommodate discrete, category-specific modules for every category. In fact, there is no limit on the number of object categories. Feature-based models can provide the flexibility needed to represent an infinite variety of objects.

In other words, the temporal-prefrontal system shown in Figure 10.21 is not likely to be a dictionary of all the semantic categories we know. There are too many of them. Rather, it may represent important features of major categories, which can index a number of categories represented in widely distributed cortical networks. We can find parts of this large region that respond more to houses than faces or more to tools than houses or cars. The 'tool'-biased regions might *index* a vast range of objects that can be used as tools – not just hammers and chisels, but perhaps computers and telephone companies. It would be very interesting to see whether one category (such as human faces) would show a 'tool use' bias if it were stated as a tool. For example, masks of human faces can be 'used as a tool' to scare people on Halloween. Such experiments might test the hypothesis that 'tool' regions might, in fact, represent a more abstract proposition such as 'can be used to accomplish a concrete goal'.

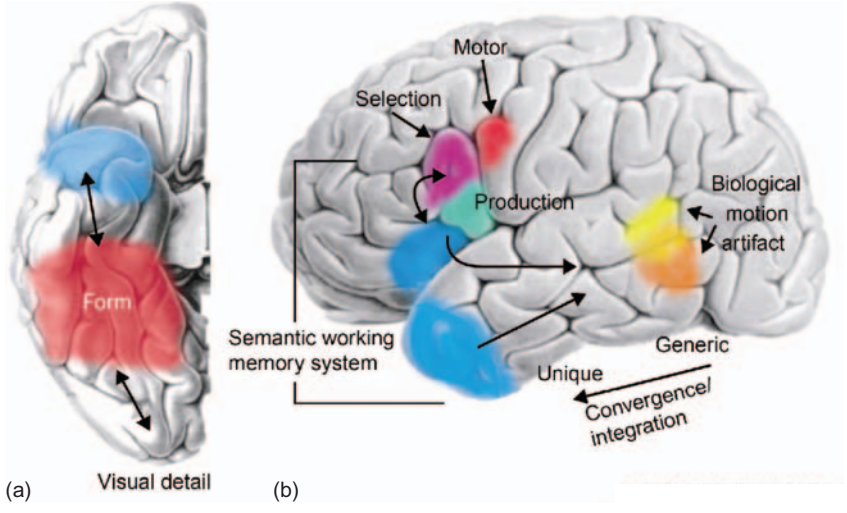


FIGURE 10.21 Brain regions involved in semantic memory. A recent summary of semantic memory location in the left hemisphere (figure on the right) and the bottom of the temporal lobe, facing upward (on the left). The spatial location of the bottom of the temporal lobe may take some study to understand clearly. Notice that there are believed to be semantic *gradients* between specific visual object areas and more abstract visual forms. Semantic working memory involves constantly looping activity between temporal and frontal regions, which must make use of subcortical connections running between them. *Source*: Martin and Chao, 2001.

Neurologists have suggested that 'object concepts are defined by sensory and motor attributes and features acquired during experience'. This appears to be a powerful organizing principle for concepts in the brain.

Possible contradictory evidence has come from single-cell studies in epileptic patients, with electrodes implanted in the temporal lobe. Some of these studies have shown very specific categorical responses, for example, to very different photos of President Clinton (Kreiman *et al*., 2002). Presumably, highly specific neuronal responding represents one node in a large network, or set of overlapping networks, having to do with political figures or famous people. It is possible that, as we learn to sample more locally in the temporal lobe, such networks containing highly specific information may be observed.

As shown in Figure 10.21, prefrontal regions close to the classical Broca's area may support a 'semantic working memory system', somewhat separate from the phonological and visuospatial components of working memory.

4.3 Abstract concepts, prototypes, and networks

Intuitively, we tend to have some misleading ideas about human cognition. One is that we carry pictures in our heads that represent the perceptual world around us. The evidence suggests instead that we tend to use visual images that are *prototypical* reminders of categories in the world, rather than accurate images of categories like chairs and movie stars. We seem to have a network of perceptual, cognitive, and motoric knowledge about chairs and their uses. Such networks can be accessed by prototypical pictures of chairs (Figure 10.22). Humans have a preference for such prototypical images, but they are not accurate depictions of all the chairs we have ever known (Rosch, 1975; Barsalou, 1999). Rather, they are special members of a category – of chairs or movie stars – which stand for the entire category. The wooden chair in Figure 10.22 may not be the average chair you have seen and used. But for the tested group that kind of visual image would come to mind more easily than the plastic or metal chairs we tend to see more often.

Barsalou (1999, 2005) has suggested that humans have a strong perceptual bias, even in dealing with abstract categories. One reason is that we do not come into the world with an understanding of abstractions. The early years of childhood are devoted to sensory, motor, and emotional exploration which, from an evolutionary point of view, are matters of survival. The developing brain may select early populations of neurons and connections before we learn adult concepts of the world.

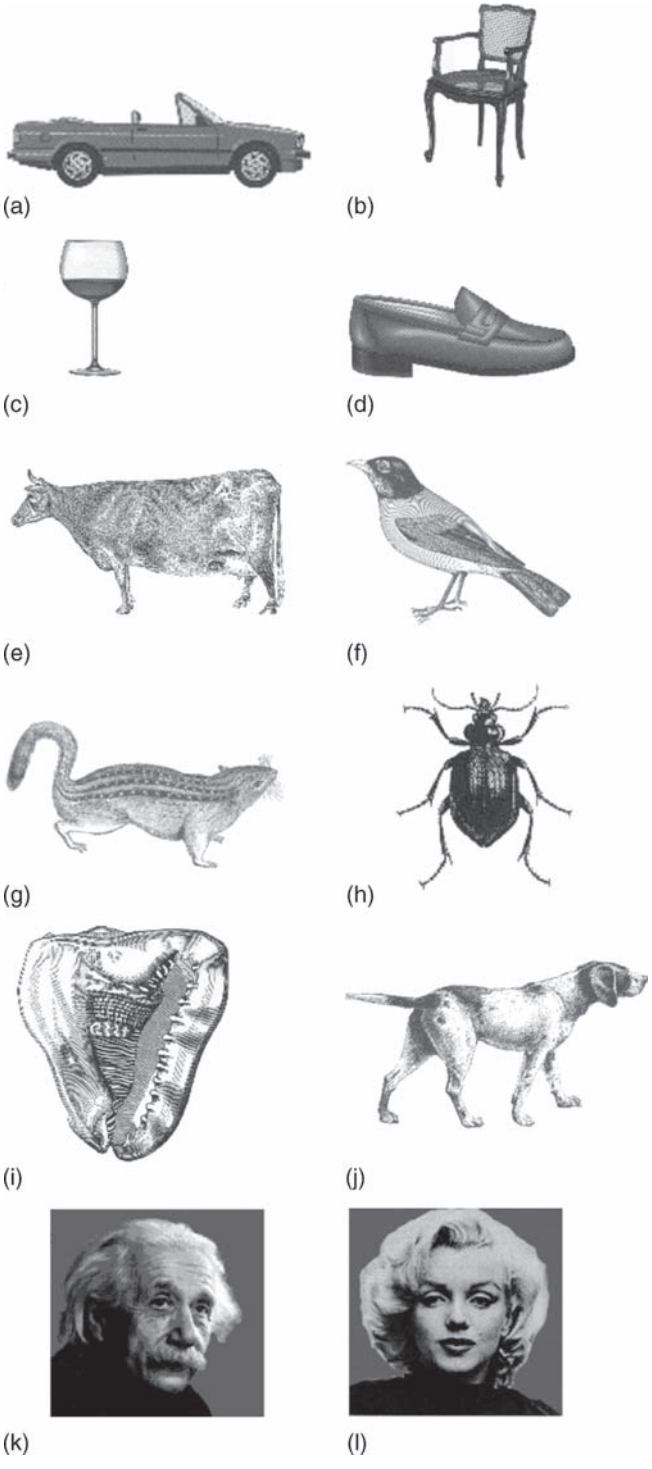


FIGURE 10.22 A set of visual prototypes tend to stand for more abstract categories. *Source*: Laeng *et al*., 2003.

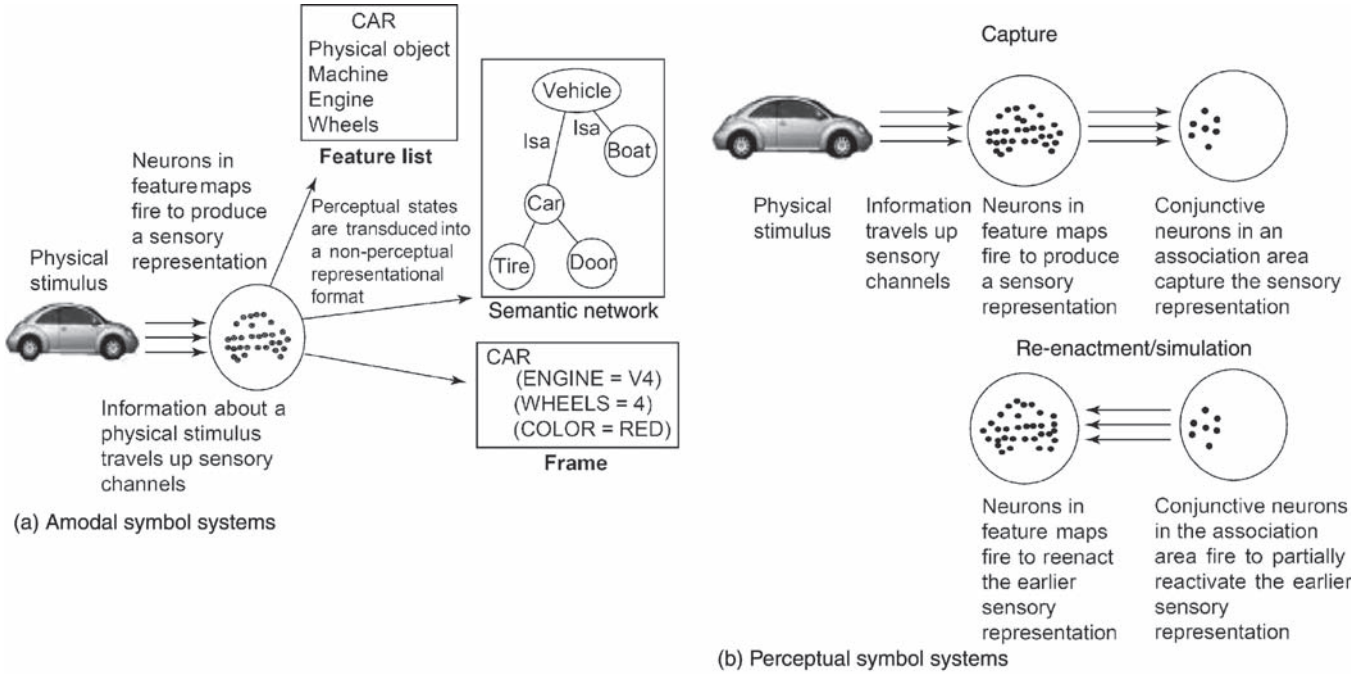


FIGURE 10.23 Amodal versus perceptual symbol systems. Barsalou (2003) has suggested that humans think by way of 'perceptual symbol systems' (a) rather than abstract categories with feature lists. (b) Such a proposal is consistent with the general tendency in the brain to build on what information it is given, especially early in life. *Source*: Barsalou, 2003.

The same point comes from studies by Barsalou and others on 'perceptual symbol systems'. Do we represent the car in Figure 10.23 the way an engineer might, as having a list of features like engines and wheels? The evidence appears to show instead that the abstract concept of a car is more dependent upon perceptual features of the appearance of the car, and a cognitive re-enactment of the actions of cars (Barsalou *et al.*, 2003).

4.4 Knowledge comes in networks

Another common intuition is that common words and concepts are simple because they often have simple names like 'car', 'brain', and 'person'. This intuition is also very misleading. Mental representations, including words, visual images, and concepts, should be viewed in terms of elaborate networks of knowledge. The cognitive evidence for such networks was extensive even before the advent of brain imaging methods. It can indeed be found in the study of science in the mid-20th century (Kuhn, 1962). Naively, we tend to think of basic scientific ideas like 'gravity' and 'molecule' as single ideas. Some philosophers therefore proposed that there must be a one-to-one relationship between the Newtonian concept of force and the physical observations that gave rise to that concept. But others pointed out that there is no observable correlate of Newtonian force at all – we only measure mass and acceleration. 'Force' is a purely inferential concept in physics (see Chapter 1). Newtonian theory is not just a list of concepts, but a network of carefully defined ideas supported by standard experiments, by predictable observations, and tied into a web of mathematical inferences. Scientific theories are therefore semantic networks, not just labeled collections of observations. The same argument applies to the words of natural language.

These points are fundamental for understanding how the brain represents knowledge. In brain imaging we do not see abstract classes of objects. Rather, we see perceptual objects in sensory regions of the brain, which gradually shade into more abstract forms of representation (see Figure 10.21). Ideas appear to be represented in the cortex in terms of complex webs of learned connectivities, rather than localized filing systems with neatly arranged conceptual categories. The brain is a very practical organ, always close to the sensorimotor and motivational world, rather than being an abstract logic machine. (The brain can do logic, of course, but most of the time it is focused on more down-to-earth processes.)

The need for semantic networks, not simple concept nodes, is important to understand when we look for the

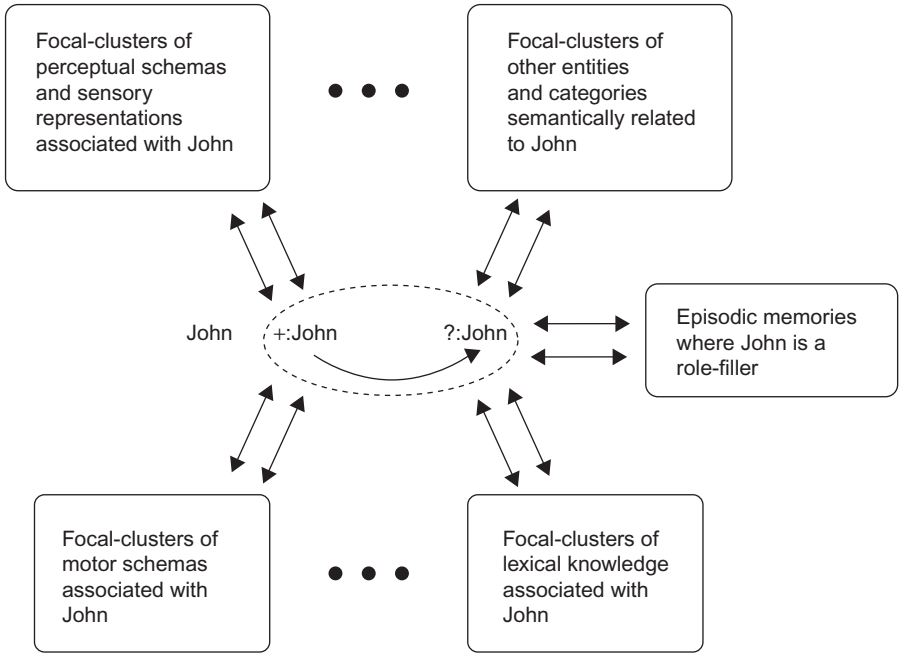


FIGURE 10.24 A proposed network for a single word. Each word in our lexicon refers to a *network* of related perceptual, semantic, motor, and lexical nodes. *Source*: Lokendra Shastri, with permission.

neural basis of cognitive units like words, ideas, and images. For example, Figure 10.24 shows how a single personal name might be represented in a neural net.

Since related concepts often share features, the same line of reasoning suggests that feature-related neurons might participate in more than one concept network. Figure 10.25 illustrates this hypothesis for the concepts of 'tiger' and 'elephant'.

It has been extremely difficult to discover specific cortical locations for specific concepts. Some of the exceptions are shown in Figure 10.26.

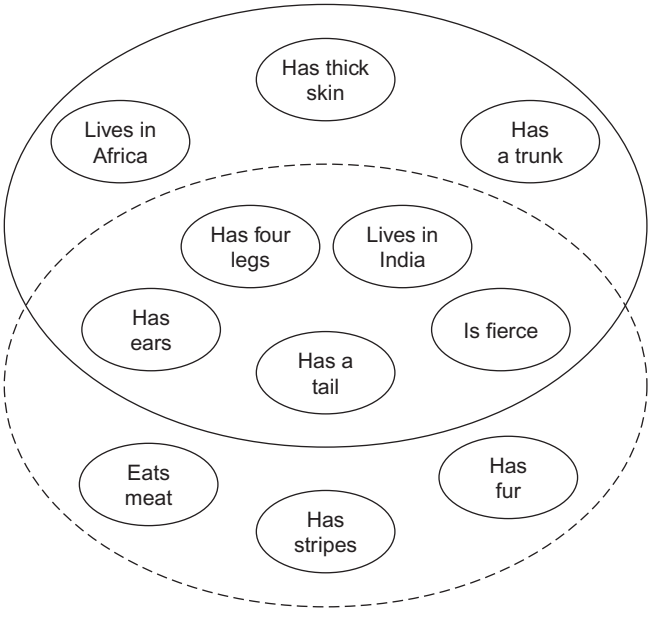


FIGURE 10.25 Overlapping semantic networks for two concepts. The brain may have feature-sensitive neurons that participate in more than one semantic network. *Source*: Hodges and Patterson, 1997.

4.5 Conceptual deficits

In general, Martin and Chao (2001) report that:

> Patients with damage to the left prefrontal cortex (LPC) often have difficulty retrieving words in response to specific cues (e.g. words beginning with a specific letter, the names of objects belonging to a specific semantic category). . . . This suggests that the LPC plays a general, albeit crucial, role in retrieving lexical and semantic information. Patients with damage to the temporal lobes often have difficulty naming objects and retrieving information about object-specific characteristics. . . . This suggests that object-specific information may be stored, at least in part, in the temporal lobes.

However, some language deficits seem to be very precise and limited. For example, in the bottom of the temporal lobe, neighboring regions seem to be devoted to somewhat different concepts, like chairs, faces, and houses. Tools, animals, and vehicles have been reported to show peak activity in separate areas. That does not mean that specific regions are the only ones involved in a concept like 'hammer' versus

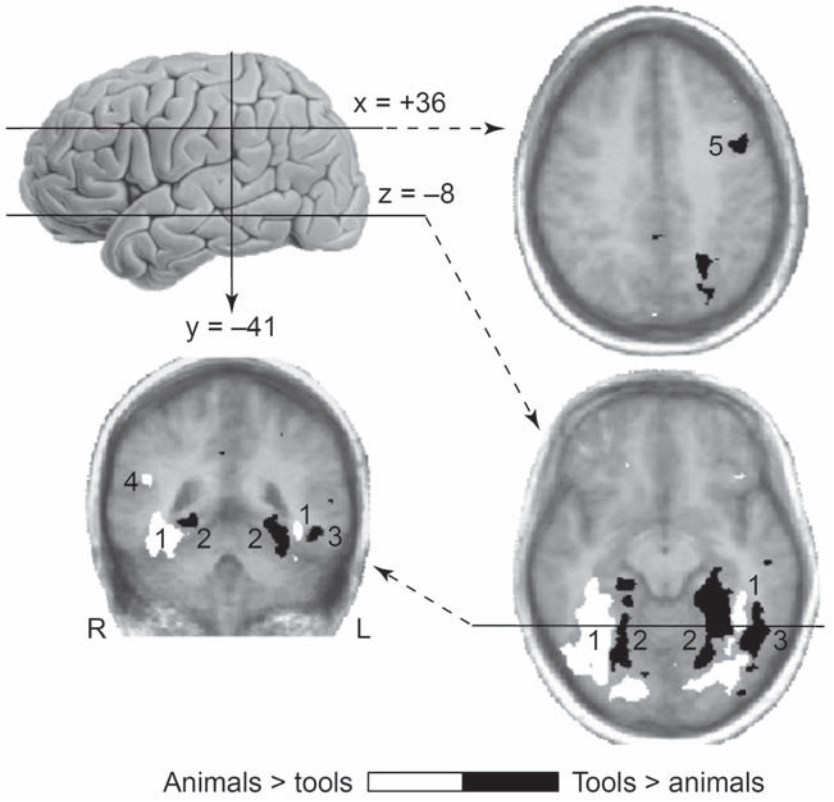


FIGURE 10.26 Areas of increased activity for animals, vehicles, tools, and vegetables. Conceptual categories are hard to find in the brain. The exceptions are very broad categories like the ones shown in this figure. Like other brain images, we can only see activation differences, between animals and tools, for example. The areas that show differential conceptual activity are in the medial temporal region. Some scientists suggest that these specific categories may serve as general indices for retrieving larger and more specific networks related to elephants and apples, rather than showing us the specific neural code for the concepts. *Source*: Caramazza and Mahon, 2003.

'bicycle'. Rather, we see peak activity in different parts of the temporal lobe, and there are cases of very local deficits as well.

Caramazza and co-workers have performed careful studies of a patient known as EW, who shows a deficit in naming animals (Caramazza and Shelton, 1998; Box 10.2). By presenting pictures with known frequency and familiarity ratings, EW's knowledge of pictured categories could be tested in a controlled way. She had greater difficulty naming animals compared to other categories. EW also had difficulty simply recognizing animal pictures, but not other categories. Her deficit was not restricted to pictures, but also extended to spoken animal names. Yet the patient performed in the normal range on complex visual picture processing, such as face recognition and picture matching.

Finally, EW had trouble with major attributes of animals, but not attributes of other objects. Given questions like 'Does a whale fly'? and 'Does a cow have a mane'? she was incorrect about a third of the time. She performed better on other categories. While the idea of specific deficits is compelling, there are alternative interpretations of the evidence (Tyler and Moss, 2001).

4.6 Judgments of quantity and number

To the surprise of many, good evidence has emerged in recent years for a specific area of parietal cortex for number naming and judgments. Dehaene *et al*. (2004) suggest that the region shown in Figure 10.27 has a special affinity for quantitative judgments, though it may have other functions as well. When we perform mental arithmetic, however, as you might expect, inner speech areas are activated, presumably because we are mentally talking through the steps of subtraction or multiplication (Figure 10.28). It would be interesting to find subjects who are skilled in using visual arithmetic, such as users of an abacus. We would not expect the phonological region to become activated for arithmetic operations in such people, but rather regions of the occipital and parietal cortex.

5.0 IMPLICIT THINKING

The story is told that as a child, Wolfgang Amadeus Mozart would tease his father Leopold (who was also his music teacher) by playing a phrase on the harpsichord and deliberately leaving it unfinished. Western

music almost always completes a series of notes or chords to end up where it started, at the tonic note of the scale. In Mozart's time that rule could not be violated. Leopold Mozart would have to get out of bed, walk downstairs, and play the sequence of notes running in his mind before he could go back to sleep. It was simply intolerable to hear an incomplete melodic series. You can get the same effect by playing a favorite recorded song, and stopping it just before it comes to a conclusion.

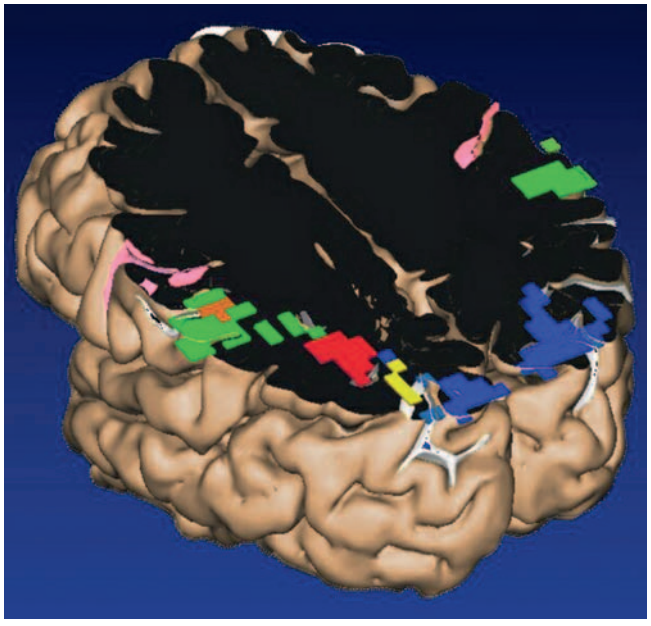


FIGURE 10.27 A network for number judgments? This parietal network was found to be involved in number and quantitative judgments, especially the intraparietal sulcus. *Source*: Dehaene *et al*., 2004.

Completion of expected sequences is one example of implicit problem solving. We do not *tell* ourselves consciously to listen until the music comes to a resolution. But once started, we feel the need to do so. The goal is implicit or unconscious, like the rules of harmony and melody. Few people can explain those basic rules, but they have powerful effects nevertheless. If we compare listening to a song to solving the Tower of Hanoi puzzle (above), music understanding is unconscious in almost all the ways the Tower problem is conscious.

Most human problem solving is a mixture of explicit and implicit ingredients. We tend to underestimate the complexity of implicit cognition, precisely because it is unconscious. In fact, it is our highly expert, overlearned habits that may be the most efficient tools for solving problems. The explicit aspect of problem solving may be better used for temporary executive functions in otherwise habitual tasks. For example, in driving a car we may be 'on automatic' much of the time, because of the routine and predictable nature of the task. But when traffic becomes dense and unpredictable, when the car tire springs a leak, or when someone is distracting us by talking, executive control of driving may be more needed. Thus, there may be a flexible tradeoff between more controlled and more automatic aspects of the act of driving. The same principles may apply to other kinds of problem solving.

5.1 Feelings of knowing

Feelings of knowing and 'fringe' or 'vague' conscious events are believed to be very common (James, 1890). These include the well-studied 'tip-of-the-tongue'

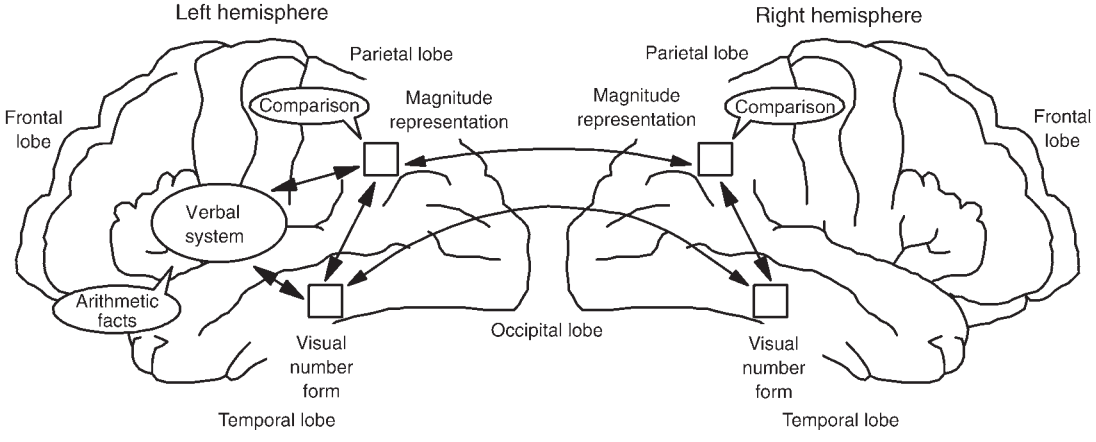


FIGURE 10.28 Mental arithmetic uses the phonological loop of inner speech. Notice the overlap in phonological tasks (such as mental rehearsal of a word list) and the subtraction task. Presumably inner speech is involved in subtraction, in this case. *Source*: Wynn in Ramachandran, 2002.

BOX 10.2 Specific conceptual deficits in patient EW

An illustrative case of category-specific semantic deficit: patient EW

To appreciate the remarkable nature of category-specific semantic deficits, consider the case of patient EW[a]. This patient presented with a disproportionate semantic impairment for the category 'animals' compared with other categories. Here we outline the empirical characteristics of EW's profile of impairment probably due to temporal lobe damage.

Picture naming

On subsets of the Snodgrass and Vanderwart (1992)[b] picture set matched jointly for familiarity and frequency, and for visual complexity and familiarity, EW was disproportionately impaired at naming animals compared with naming non-animals (Table 10.1). This indicates that EW's category-specific deficit for picture naming cannot be attributed to uncontrolled stimulus variables (e.g. Stewart *et al.*, 1992; Funnel & Sheridan, 1992;[c, d]).

EW's picture-naming performance was not only quantitatively different for animals and non-animals but was also qualitatively different. For animals, EW either named the picture incorrectly or did not recognize the picture, whereas for non-animals, EW recognized the picture but could not retrieve the name (Figure 10.29(a)).

EW's naming deficit was restricted to the category 'animals' and did not extend to the other living things such as 'fruit/vegetables', for which performance was at ceiling.

Sound identification

EW was also impaired at naming animals compared with non-animals based on their characteristic sounds (8/32; 25% correct versus 20/32; 63% correct: z 3.06, $P < 0.05$), indicating that the naming impairment is not restricted to visual input.

Object decision

EW was asked to decide ('yes' or 'no') whether a depicted object was real (see Figure 10.29(b) for examples of stimuli).

TABLE 10.1 EW's picture-naming performance for matched sets of items[b]

	Matched familiarity and frequency		Matched visual complexity and familiarity	
	Animals	Non-animals	Animals	Non-animals
EW	12/22 (55%)	18/22 (82%)	7/17 (41%)	16/17 (94%)
Controls	11/11 (100%)	10.8 (98%)	16.6/17 (98%)	16/17 (94%)
Range	11	10–11	16–17	16–17

Performance on this task is interpreted as reflecting the integrity of the visual/structural description system (i.e. the modality-specific input system that stores representations corresponding to the form or shape of objects, and which is used to access conceptual information). EW performed significantly below the normal range for differentiating real from unreal animals (36/60: 60% correct; control mean: 54/60: 90%) but within the normal range for differentiating real from unreal non-animals (55/60: 92% correct; control mean: 50.5/60: 84% correct).

Parts decision

EW was asked to decide which of two heads (or parts) went with a headless body (or object missing a part) (see Figure 10.29(c) for examples of stimuli). EW was severely impaired on this task for animals (60% correct; normal mean = 100%) but performed within the normal range for artifacts (97% correct; normal mean = 97%).

Visual processing

EW performed within the normal range on complex visual processing tasks, such as visual matching and face recognition. These data indicate that EW does not have a general deficit for processing visually complex stimuli

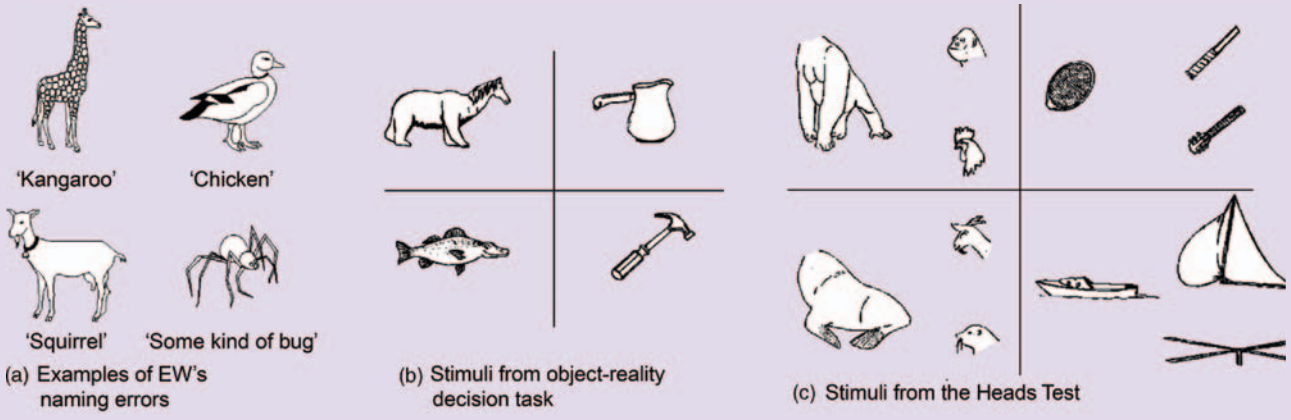


FIGURE 10.29 (a) Examples of EW's naming errors. (b) Examples of stimuli from the object-reality decision task. (c) Examples of objects from the 'Parts decision test' or 'Heads test'.

(*Continued*)

BOX 10.2 (Continued)

and suggest that the impairment for object reality decision for animals is categorically based.

Central-attribute judgments

EW was asked to decide whether a given attribute was true of a given item (see Table 10.2 for examples of stimuli). EW was severely impaired for attributes pertaining to animals (65% correct; control range 85–100%) but within the normal range for attributes pertaining to non-animals (95% correct; control range 86–100%). EW was equivalently impaired for both visual/perceptual and functional/associative knowledge of living things (65% correct for both types of knowledge) but within the normal range for both types of knowledge for non-animals (visual/perceptual: 93.5% correct; control range 86–100%; functional/associative: 98% correct; normal range 92–100%). EW's performance on answering central-attribute questions indicates that her deficit is not restricted to production.

TABLE 10.2 Examples of central-attribute questions

Visual/Perceptual	Functional/Associative
Does a cow have a mane?	Does a whale fly?
Does a whale have a large tail fin?	Does an eagle lay eggs?
Does a whale have eight legs?	Is a cow a farm animal?

References

a Caramazza, A., & Shelton, J. R. (1998). Domain-specific knowledge systems in the brain: the animate-inanimate distinction. *Journal of Cognitive Neuroscience*, *10*, 1–34.

b Snodgrass, J., & Vanderwart, M. (1992). A standardized set of 260 pictures: norms for name agreement, familiarity, and visual complexity. *Journal of Experimental Psychology. [Human Learning]*, *6*, 174–215.

c Stewart, F., *et al*. (1992). Naming impairments following recovery from herpes simplex encephalitis. *The Quarterly Journal of Experimental Psychobiology A*, *44*, 261–284.

d Funnel, E., & Sheridan, J. S. (1992). Categories of knowledge? Unfamiliar aspects of living and nonliving things. *Cognitive Neuropsychology*, *9*, 135–153.

BOX 10.3 Associative visual agnosia

Case study of associative visual agnosia

The subject was a 47-year-old man who had suffered an acute loss of blood pressure with resulting brain damage. His mental status and language abilities were normal, and his visual acuity was 20/30, with a right homonymous hemianopia (blindness in the right visual hemifield). His one severe impairment was an inability to recognize most visual stimuli. For the first 3 weeks in the hospital, the patient could not identify common objects presented visually and did not know what was on his plate until he tasted it. He identified objects immediately on touching them.

When shown a stethoscope, he described it as 'a long cord with a round thing at the end' and asked if it could be a watch. He identified a can opener as a key. Asked to name a cigarette lighter, he said, 'I don't know' but named it after the examiner lit it. He said he was 'not sure' when shown a toothbrush. He was never able to describe or demonstrate the use of an object if he could not name it. If he misnamed an object, his demonstration of use would correspond to the mistaken identification. Identification improved very slightly when given the category of the object (e.g. something to eat) or when asked to point to a named object instead of being required to give the name. When told the correct name of an object, he usually responded with a quick nod and often said, 'Yes, I see it now'. Then, often he could point out various parts of the previously unrecognized item as readily as a normal subject (e.g., the stem and bowl of a pipe

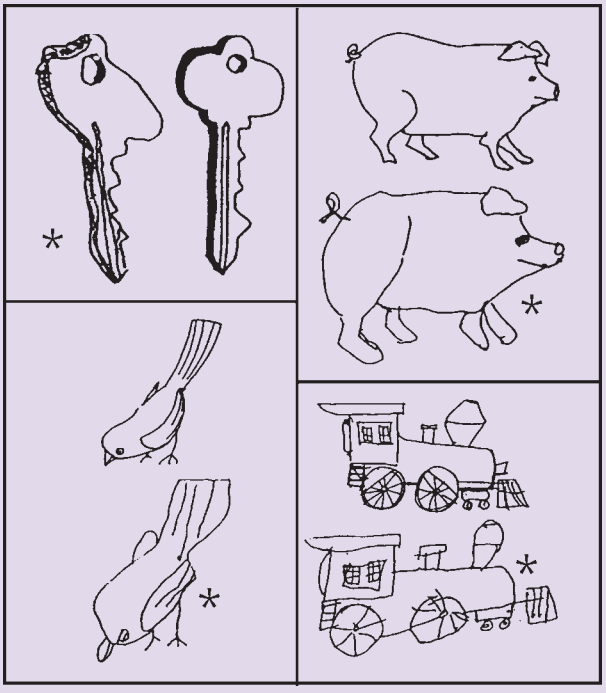


FIGURE 10.30 Visual agnosia. A patient with associative visual agnosia was able to copy the everyday pictures above, but not to name them (Rubens and Benson, 1971). *Source*: Squire *et al*., 2003.

and the laces, sole, and heel of a shoe). However, if asked by the examiner, 'Suppose I told you that the last object was not really a pipe, what would you say'? He would reply, 'I would take your word for it. Perhaps it's not a pipe'. Similar vacillation never occurred with tactilely or aurally identified objects.

After he had spent 3 weeks on the ward, his object-naming ability improved so that he could name many common objects, but this was variable; he might correctly name an object at one time and misname it later. Performance deteriorated severely when any part of the object was covered by the examiner. He could match identical objects but could not group objects by categories (clothing, food). He could draw the outlines of objects (key, spoon, etc.) that he could not identify.

He was unable to recognize members of his family, the hospital staff, or even his own face in the mirror. Sometimes he had difficulty distinguishing a line drawing of an animal face from a man's face but always recognized it as a face. The ability to recognize pictures of objects was impaired greatly, and after repeated testing he could name only 1 or 2 of 10 line drawings. He was always able to name geometrical forms (circle, square, triangle, cube). Remarkably, he could make excellent copies of line drawings and still fail to name the subject (Figure 10.30). He easily matched drawings of objects that he could not identify and had no difficulty discriminating between complex nonrepresentational patterns, differing from each other only subtly. He occasionally failed in discriminating because he included imperfections in the paper or in the printer's ink. He could never group drawings of objects by class unless he could first name the subject. Reading, both aloud and for comprehension, was limited greatly. He could read, hesitantly, most printed letters but often misread 'K' as 'R', and 'L' as 'T' and vice versa. He was able to read words slowly by spelling them aloud.

a Hillary R. Rodman, Luiz Pesson, & Leslie G. Ungerleider. Excerpted from Rubens and Benson, 1971.

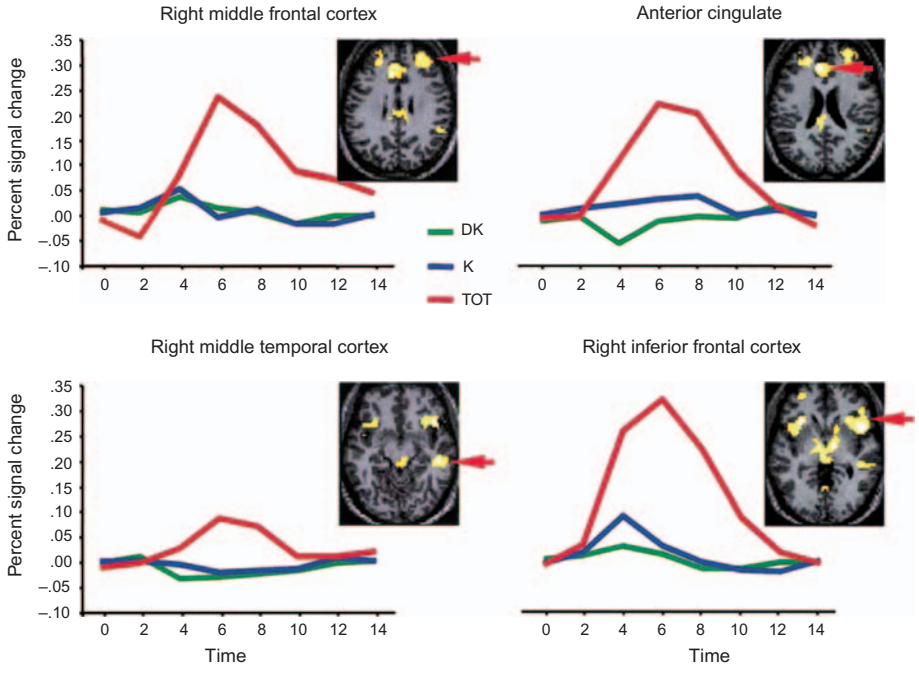


FIGURE 10.31 Effortful thought in word finding. These figures show both the location of the increased activity in the 'tip of the tongue' state, and their time course (using event-related potentials). Notice that the classical executive regions are again active. While these regions are not normally viewed as contributing to conscious experience, the fact that tip-of-the-tongue states can be reported in a verifiable manner suggests that they are at least 'fringe' conscious. *Source*: Maril *et al.*, 2001.

feeling and 'feelings of knowing'. It is easy to induce a tip-of-the-tongue state. All we need to do is provide people with definitions of fairly rare but known words, and ask them if they feel they almost have the answer, but not quite. Effective questions might include 'what is the name of a vegetarian dinosaur'? or 'what are two words for the technology for making artificial limbs'?

Such subjectively vague but reportable events have been found to guide intuitive problem solving, including verbal and pictorial problems (Bowers *et al.*, 1990), promote persistence in memory search during tip-of-the-tongue states (Brown and MacNeill, 1966), guide memory retrieval and persistence (Metcalfe, 1986), and influence judgment tasks and decision making (Yzerbyt *et al.*, 1998). Only a few brain studies are available, but Maril *et al.* (2001) have shown that the tip-of-the-tongue state, which can be easily induced, showed high activity in prefontal regions, the same cortical areas that are associated with persistence in problem solving (Duncan and Owen, 2000) (Figure 10.31).

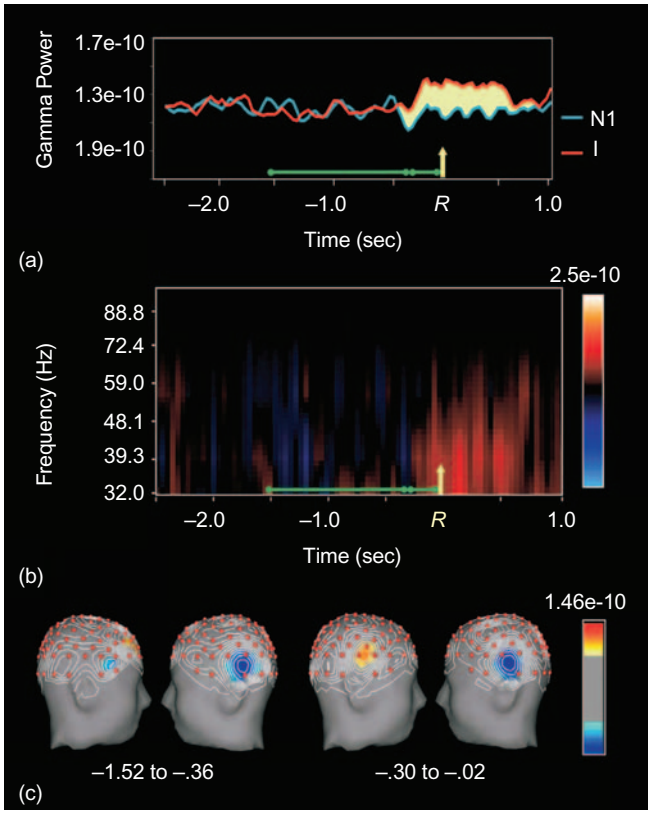


FIGURE 10.32 Sudden insight in problem solving. Alpha and gamma density in decomposed EEG at the moment of insight in a word association task. Notice that just before a correct response, alpha density declines just as gamma density increases. Gamma activity is thought to be due to active and synchronized processing in a network of related regions needed to solve the problem. In (c), immediately before the solution (marked with minus values in seconds), there is an EEG shift to the left hemisphere. *Source*: Jung-Beeman *et al*., 2004.

There is good evidence that spontaneous thought is problem oriented, even if the goal of the mental process is not explicit (Greenwald *et al*., 2002). The contents of spontaneous thoughts are often described as one's 'current concerns'. Social psychology experiments have found that one can experimentally prime some current concern, such as relationship arguments, by showing videos that 'play out' those concerns. Thus, college students who rated their relationships with their parents as conflictual reported more common thoughts related to conflict when they were provoked by a video.

However, similar problem solving patterns are found to be very common when careful studies have been performed on the routine 'stream of consciousness' (Singer, 1994). 'Jumps' in the flow of thought are apparently routine, and they can be elicited experimentally in tip-of-the-tongue experiments (see Figure 10.31) and the well-known Remote Associates Test (Kihlstrom, 1996). Sudden insight can also be elicited experimentally, as shown in Figure 10.32.

6.0 SUMMARY AND CONCLUSIONS

Working memory is the domain of problem solving. Completely explicit problem solving is probably rare in the natural world. However, explicit puzzles like the 'tower problems' are quite sensitive to frontal lobe damage and to other impairments of problem solving capacities, like drowsiness, drug effects, boredom, cognitive overload, or distraction. Thus, explicit problem solving tasks are useful indices of brain functioning. In addition, tasks like the Wisconsin Card Sorting Test can be used to set up 'fixed' expectations about a puzzle, to allow testing of cognitive flexibility in the face of unexpected changes in tasks. Subjects with prefrontal impairments are again vulnerable to such task shifting.

Because of capacity limits of working memory, attention, conscious processes, and voluntary control, a major strategy in problem solving is to use chunking or other long-term memory components to shift routine aspects of problem solving to the large-capacity memory systems. Chess experts, for example, know a great many predictable chess positions from memory, freeing their working memory capacity to deal with novel and unpredictable aspects of a chess game. Long-term semantic memory is still rather mysterious in its details, but is known to use temporal and prefrontal regions, as well as the episodic learning capacities of the medial temporal lobe.

While implicit thinking is efficient, it is also vulnerable to rigidity and lack of flexible control. An optimal problem solving strategy mixes explicit and implicit approaches. Fringe-conscious judgments are commonly encountered in tasks like 'feelings of knowing' and 'tip of the tongue'. These tasks may give us metacognitive knowledge of ongoing implicit problem solving processes. They are now believed to activate the classical executive regions of the prefrontal cortex.

7.0 DRAWINGS AND STUDY QUESTIONS

1 Fill in the boxes in Figure 10.33. Notice that the boxes are paired. One of each pair refers to a brain region and the other to a major possible function discussed in this chapter.

2 Do the same for Figure 10.34. What is the relationship between the two figures?

3 Give an example of 'chunking' in an expert task. Why is chunking necessary in the human brain?

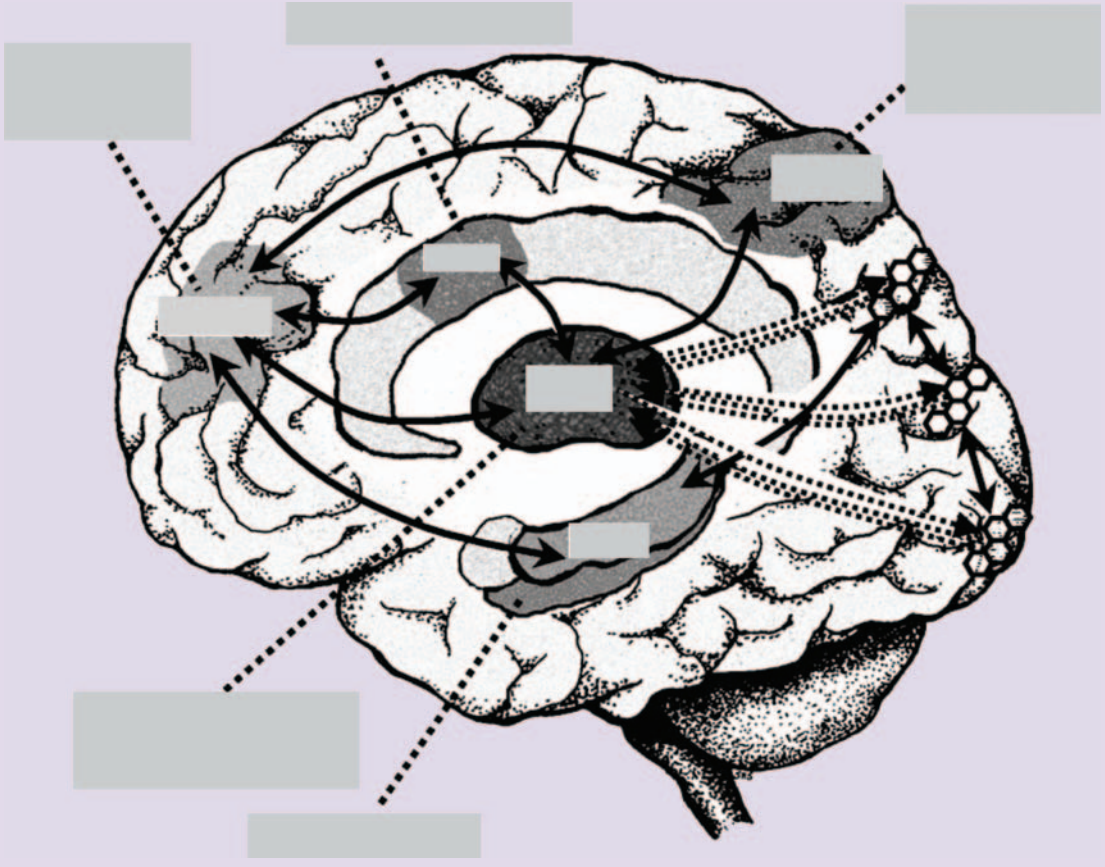


FIGURE 10.33

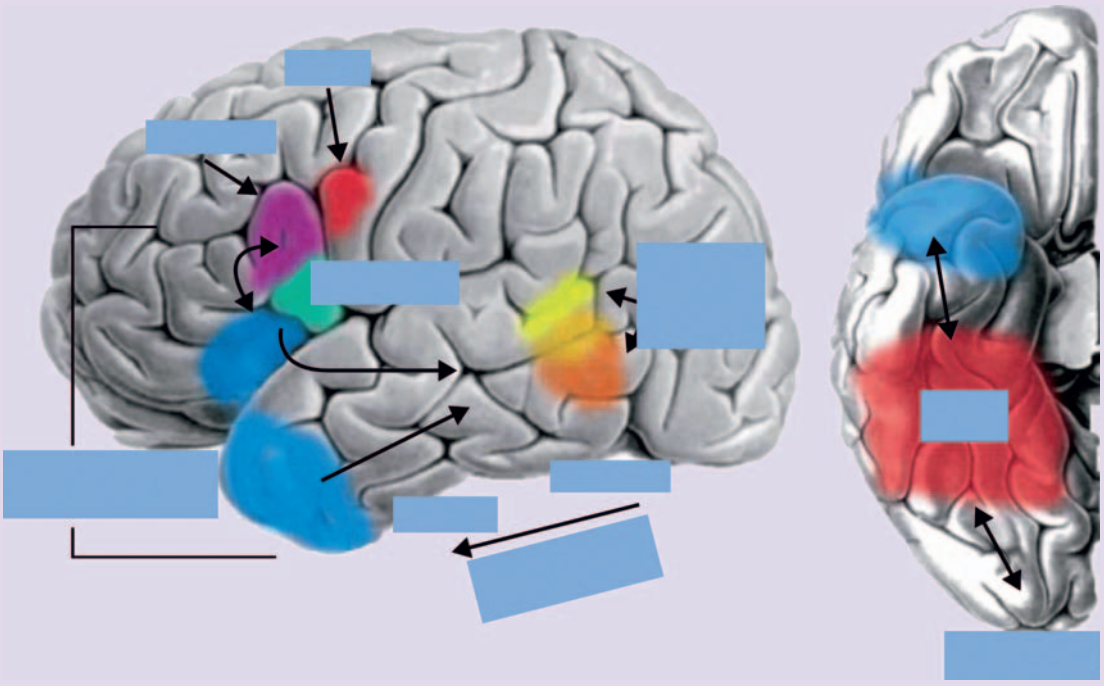
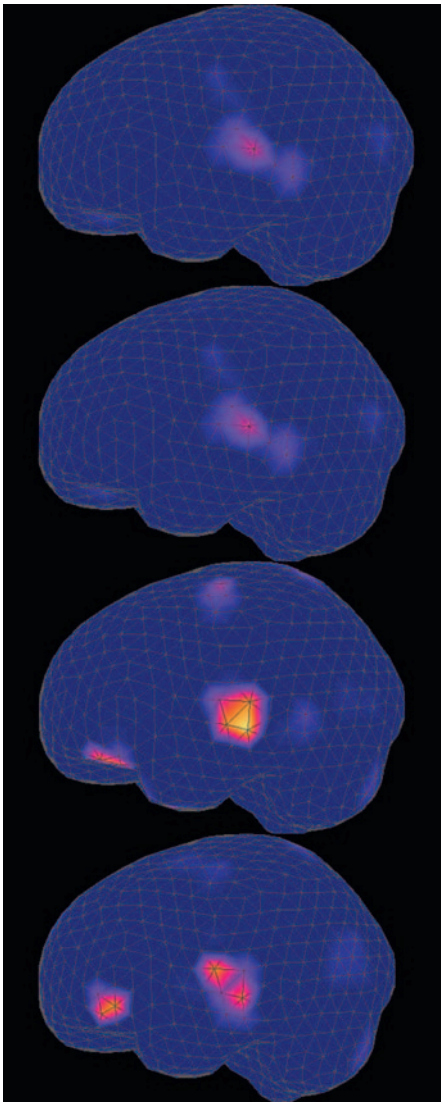


FIGURE 10.34 Label the brain regions and detail the memory processes they are theorized to subserve.

Mr Broca, on the occasion of this report, presented the brain of a fifty-one-year-old man who died in his care at Bicêtre hospital, and who had lost the use of speech. . . . When the patient was admitted to Bicêtre, at the age of 21, he had lost, for some time, the use of speech; he could no longer pronounce more than a single syllable, which he ordinarily repeated twice at a time; whenever a question was asked of him, he would always reply tan, tan, in conjunction with quite varied expressive gestures. For this reason, throughout the hospital, he was known only by the name of Tan.

Pierre Paul Broca (1861), Loss of Speech, Chronic Softening and Partial Destruction of the Anterior Left Lobe of the Brain, First published in *Bulletin de la Société Anthropologique*, **2**, 235–238. Translation by Christopher D. Green http://psychclassics.yorku.ca/Broca/perte-e.htm



Brain activity to a single spoken word (starting with the first panel at the top). Notice the fast spread of activity beyond the auditory cortex. By the third image down, there is spread forward to the left inferior frontal gyrus (L-IFG), as well as central sulcus, parietal cortex, and even the occipital pole. These MEG scans show mismatch negativity (MMN), a large wave of electromagnetic activity in response to an unexpected stimulus. *Source*: Pulvermüller *et al.*, 2006.

CHAPTER

11

Language

OUTLINE

1.0 INTRODUCTION

Language is the foremost tool of human thought and culture. It is also one of the major landmarks of child development, with no close parallel in other species. Before our fourth birthday we have solved the problems of understanding our first phonology, our first basic lexicon, and syntax. New words are acquired at a very fast pace during those years. While our understanding of syntax is still not fully settled, children acquire it with little visible difficulty. In addition, young children know how to use their emerging language skills to accomplish important goals (Figure 11.1). Even before they acquire language they have a good understanding of the world around them. These are achievements of brain development, enabled by good caregivers, helped by cognitive and emotional stimulation and experience, and of course by the cultural gift of a native language.

To illustrate the scientific questions posed by language, it is interesting to ask someone to repeat a sentence he or she has just heard. You may be surprised: people can rarely remember a sentence verbatim after only a few seconds. It's not that we have poor memories, but rather that we tend to retain the meaning, not the words of what we hear (Sachs, 1967). Most people can therefore give us a *paraphrase* of what they hear – a different sentence with a similar meaning – but not the

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

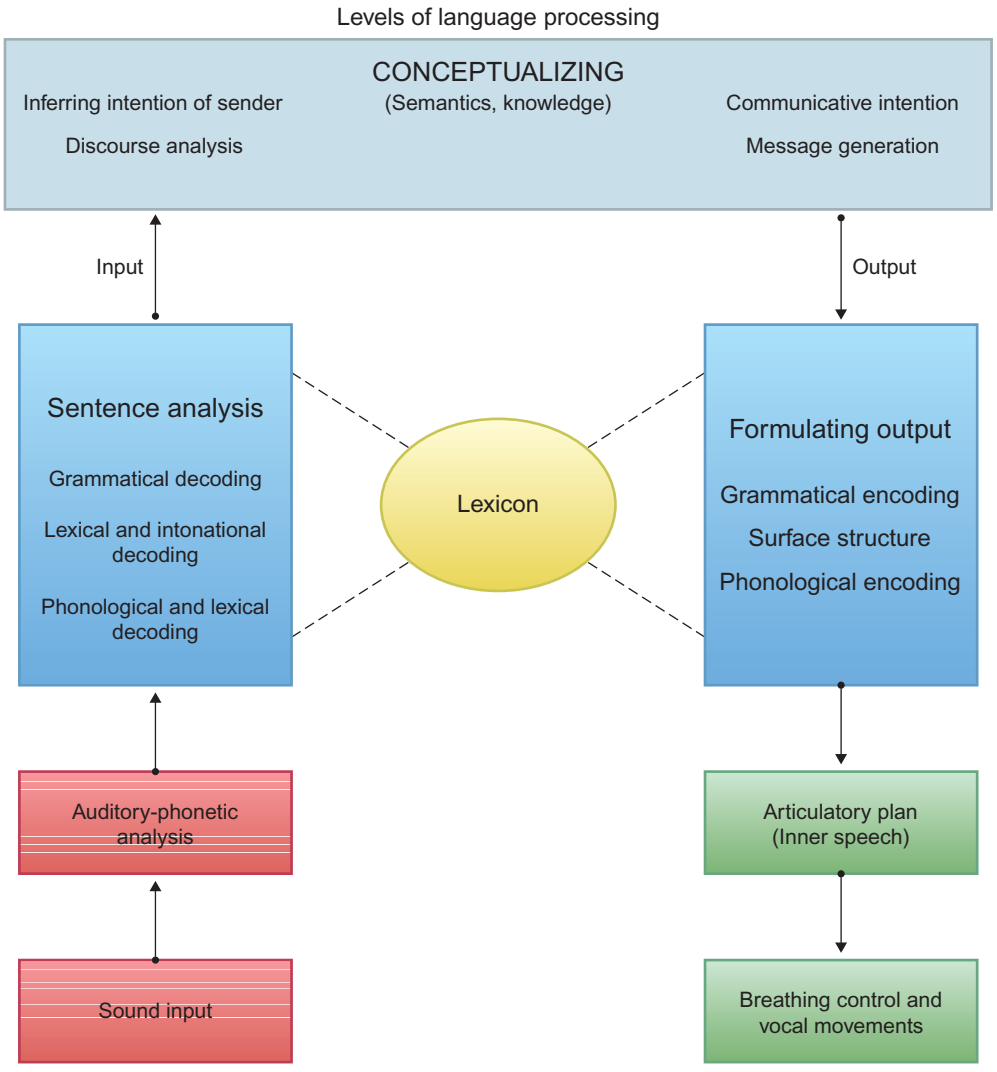


FIGURE 11.1 Levels of language – analysis and production. A sketch of levels of language analysis and production. Each level is highly complex, but is processed by skilled speakers largely unconsciously and in seconds. *Source*: Baars, adapted from Miller, 1991.

original sentence. As soon as speech is understood, we tend to forget its 'outer form'. It has served its purpose.

Thus, within a few seconds, sound input seems to go through the following analyses:

- Acoustical analysis – turning sounds into linguistic elements such as phonemes; phoneme coding and serializing, to construct syllables and morphemes (meaningful units)
- Lexical identification – assigning words to the input, chosen from a vocabulary of tens of thousands of words
- Syntactic analysis – identifying nouns, verbs, and other grammatical categories, and constructing a syntactic frame
- Semantics – building the semantic network of the lexical and syntactic structure
- Discourse and conversational reference – how does the identified meaning relate to previous concepts in the conversation or discourse?
- Pragmatic and social inferences – what is the speaker's goal, and what does it mean for my goals?

2.0 THE NATURE OF LANGUAGE

As Barrett *et al*. (2003) have put it, monkeys think 'what now'?, but apes think 'what if'? That is, primates

with larger frontal cortices can think about imagined events, not in the here-and-now, but in the there-and-then as well. It seems like a small difference, but language and a host of language-based cultural developments have turned it into moon landings and toothbrushes, and perhaps some developments that are not quite as pleasant. The evolutionary history of the human species is, in many ways, the history of the deployment of language in pursuit of personal and cultural ends.

BOX 11.1 Ambiguities exist at all levels of language

Figure 11.1 gives the impression that there is a point-to-point relationship between sound input and phonetic analysis or between words and their meanings. This is an impression expert speakers tend to have, and it is wrong. Language is rife with ambiguities at every level of analysis, both in input and output. That is to say, there are *choice-points* in processing (see Chapter 10). For example, most common words have more than one meaning, so that the mapping between the lexicon and the conceptual representation at the top of Figure 11.1 always involves alternatives. There are also frequent ambiguities in acoustical analysis, and famous syntactic ambiguities, like the tree diagram of a surface structure ambiguity in Figure 11.2 (Chomsky, 1957).

A recent estimate of lexical ambiguity suggests an average of two high-frequency interpretations per word (Miller, 1991). More common words tend to have more meanings, so that the word 'set', for example, has more than two dozen senses according to the *Oxford English Dictionary* (Simpson and Weiner, 1989).

Choice-points also exist in the production of speech and language. We tend to become conscious of them in creative writing, when we perceive a choice between two words with slightly different meanings. Synonyms and paraphrases create choice-points in language production, while ambiguities at different levels of analysis create choice-points in language input.

Choice-points in the flow of processing require resolution, often using different levels of analysis. They turn a simple flow from one linguistic level to another into a maze, which tends to lead to a 'combinatorial explosion'. That is, for n binary choice points, the number of possible paths through the maze rises exponentially as 2^n. This number rises so quickly that computer-based speech and language interpretation has proven to be very difficult.

The general solution is called 'top down' or 'expectation-driven' processing. That is, when we encounter an ambiguous word like 'set' in 'Please set the table', we can tell from the semantic context that dishes are involved. In 'Please, set an example', something very different is intended. In these cases, semantic knowledge is needed to resolve the ambiguity. Thus, higher levels of analysis are needed to resolve choice-points at lower levels. The 'hierarchy' of language, like the processing hierarchy of vision (Chapter 3) requires flow of information in all directions. The flow of information might look something like Figure 11.3.

In general, as Mesalum (1990) has written:

> Cognitive problems are not resolved by a sequential and hierarchical progression toward predetermined goals but instead by a simultaneous and interactive consideration of multiple possibilities and constraints until a satisfactory fit is achieved. The resultant texture of mental activity is characterized by almost infinite richness and flexibility. According to this model, complex behavior is mapped at the level of multifocal neural systems rather than specific anatomical sites, giving rise to brain-behavior relationships that are both localized and distributed.

Top-down or expectation-driven processing appears to be a universal property of the cognitive brain.

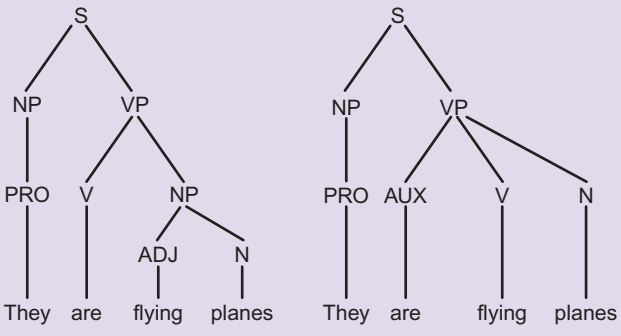


FIGURE 11.2 A syntactic ambiguity. There are two ways to understand the sentence, 'They are flying planes', either as 'The pilots are flying planes' or 'The planes are flying'. The assignment of the subject (they) is ambiguous, and as a result, the underlying structure is as well. Pronouns like 'they' are a rich source of ambiguity in language, since they take the referent for granted. Skilled speakers are rarely conscious of such ambiguities, but newcomers to any language community tend to misunderstand them. Syntactic ambiguities are just one kind of choice point in language analysis.

(*Continued*)

BOX 11.1 (Continued)

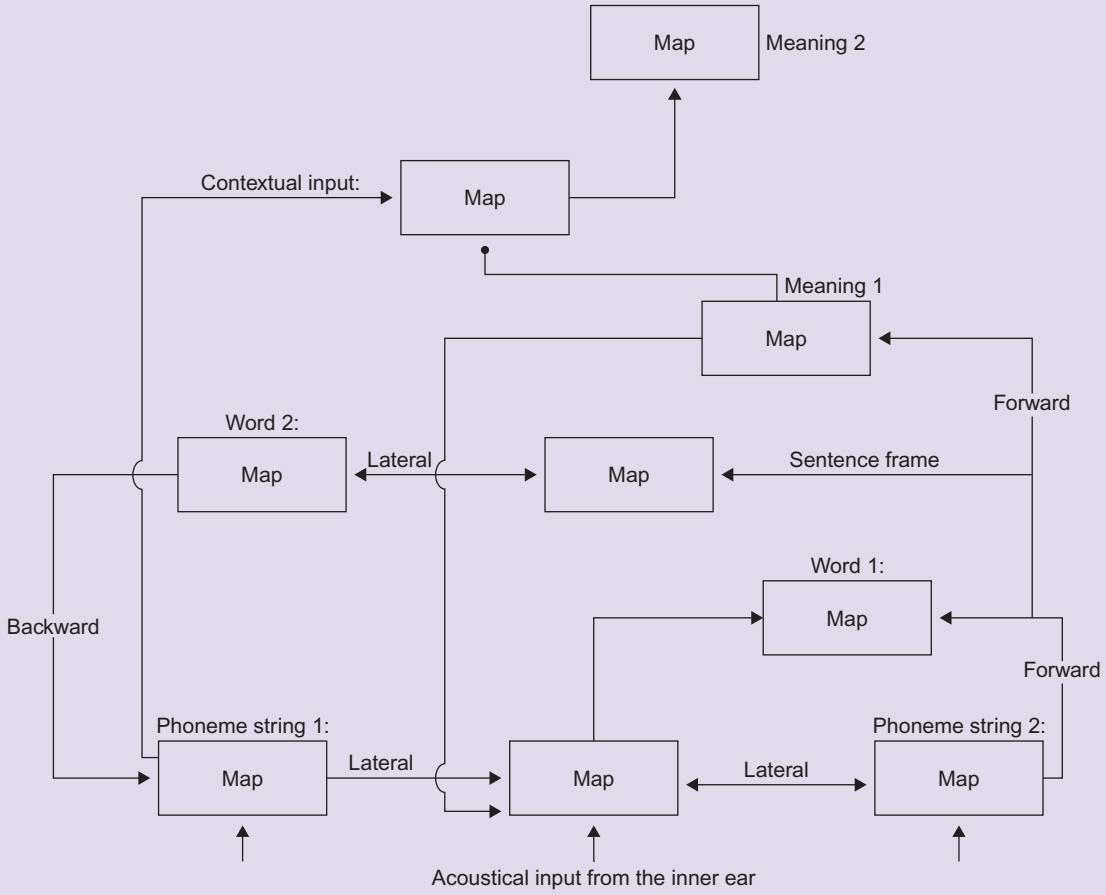


FIGURE 11.3 Information does not flow point-to-point in the language hierarchy. Like the visual processing hierarchy of Chapter 3, the physical speech signal presents the brain with a great many choice-points, both in input and output. In input processing there are numerous ambiguities of sound, word meaning, and syntax that are believed to be resolved by expectations from other levels of analysis throughout the hierarchy. There is no strict bottom-up flow in language, just as there is no simple one-to-one mapping in vision. The same point applies to output processing. *Source*: Baars.

2.1 Biological aspects

Virtually all humans learn to speak in the first several years of life, and no other species does. There are interesting exceptions, like the chimps and gorillas, who are able to acquire sign language by observational learning and training early in life. But, as a species, other living primates do not acquire language, while humans do. This is not to minimize the special capacities of bonobos and other primates, nor of other species, like the African grey parrots Alex and Arthur (Pepperberg, 2002); it is simply that language appears to be a human capacity for which we are biologically and culturally prepared. That is why we are good at it.

Children acquire language in predictable stages, and even develop their own 'creoles', true rule-governed languages, when they grow up in mixed-language communities without a single dominant language (see Box 11.2). After childhood it becomes more difficult to acquire the skills of a native speaker. Spoken language is a complex biological overlay over pre-existing vocal and auditory physiology. Language production tends to be lateralized to the dominant hemisphere (usually on the left side), though early brain damage can cause a shift to the non-dominant side (Chapter 1). The gene *FOXP2* apparently needs to be expressed accurately for normal human speech to develop, although that gene

is widely found throughout vertebrate species (Vargha-Khadem *et al*., 2005).

Repeating a sentence requires specific brain regions, assuming that the brain has developed normally. The best-known examples are Broca's and Wernicke's areas (Chapter 1), but speech and language recruit much wider cortical and subcortical activity. 'Language cortex' has only become specialized for speech within hominid evolution, less than 3 million years out of the 200 million years of mammalian evolution. Prior to hominids, Broca's area may have been involved with vocal tract control for other purposes: it is located, after all, immediately adjacent to the mouth and tongue control areas of the motor homunculus. Many ingredients of spoken language, like hearing and vocal control, must have emerged very early. But there is speculation that the full panoply of language abilities may have become available in a much shorter time span than 3 million years, perhaps as short as 30–100 000 years. Certainly, the working vocabulary of living languages seems to have expanded considerably in recent history, although syntax may have become simpler.

All these points suggest that speech and language involve biological preparedness, in much the way that manual dexterity, vision, brain development, and social relationships do. Like other genetic influences, this one is enormously interactive. Which language we acquire in childhood, how well we learn it, what vocabulary (and consequently conceptual system) we acquire, and many other variables depend upon our experiences. Nevertheless, the biological substrate of language is an important source of insight, as we will see. It does not reduce humans to some simpler living species, but rather should be taken to emphasize the enormous complexity and adaptive significance of language. Our cultural and personal accomplishments are heavily dependent upon the biological gifts of our species.

Chapter 1 touched on the discovery of the brain areas for speech production and perception in the 19th century, by Pierre-Paul Broca and Carl Wernicke, respectively. However, their findings with a small number of brain-damaged patients touched off more than a century of debate on the question of localization of language in the brain. That debate continues today, often involving neural net models of language functions, for example, and sophisticated brain recording methods (Chapters 3 and 4).

Figure 11.4 shows the classical understanding of Broca's area for speech production, and Wernicke's area for speech perception and comprehension. In addition, physicians in the 19th century discovered a number of other aphasias (language deficits). The best known of these is conduction aphasia, associated with a deficit of the arcuate fasciculus, the 'arched little bundle' running between Broca's and Wernicke's areas (Catani and Ffytche, 2005). One of the most important developments today is the ability to study the large white matter tracts that run between cortical areas, and which fill by far the greatest amount of space in the hemispheres. Tractography (Chapter 4) and other methods for studying brain connectivity in the living brain should make it possible to learn much more about both cortical specializations and their connections in the next several years.

Wernicke's area abuts the auditory cortex in the Sylvian fissure and superior temporal gyrus (STG in Figure 11.4). Broca's area is immediately adjacent to the mouth and vocal tract regions of the motor cortex. Things have gotten a lot more complex in our understanding of these regions, but it is useful to realize that the location of these areas in those particular neighborhoods makes functional sense.

In 1861, when Broca discovered patients with damage to the left inferior frontal gyrus (L-IFG), which is now called Broca's area, a great debate broke out among neurologists who found it hard to find patients with exactly the same damage and the same symptoms. That debate lasted well into the next century. We might expect the debate to be resolved with the use of sophisticated brain imaging methods, or with direct cranial stimulation studies of hundreds of patients in open brain surgery (Penfield and Roberts, 1959; for a review, see Ojemann, 2003). Surprisingly, it has not. Debates about localization of function continue today.

That is not to say that nothing has been learned in more than a century of research. Most scientists believe that Broca's area is necessary for normal speech production. But a lot more is going on in this part of the brain than previously suspected, and there are cases of damage to Broca's area that do not show the classic inability to speak. As improving neuroimaging methods are able to examine smaller and smaller regions of cortex, new subdivisions of the left inferior frontal gyrus (LIFG) are constantly being proposed.

The brain doesn't file its memory stores in neat, separate locations. However, there may be a general tendency for long-term functions to activate related sensory, motor, motivational, and language regions. The cortex has numerous very local connections within single vertical columns and sets of columns; it has slightly more remote connections between neighboring regions of larger size; and it has a vast highway

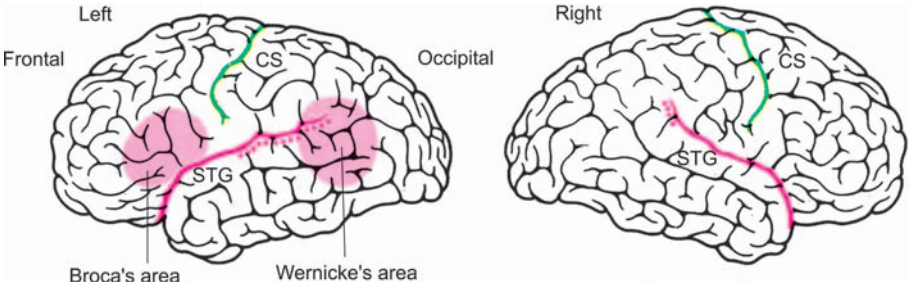


FIGURE 11.4 Classical language regions of cortex. The traditional location of Broca's and Wernicke's areas of the left hemisphere, based on neurological patients showing production and comprehension deficits. The right hemisphere has receptive language functions that are not shown here. (STG: superior temporal gyrus; CS: central sulcus.) *Source*: Standring, 2005.

system of remote connections coursing from one end of the brain to the other, from the posterior to anterior poles, from right to left hemispheres, and flowing upward and downward into the sensory and motor apparatus of the cranial nerves and the spinal cord (see Chapter 5). This kind of highly interconnected system looks more like the world-wide web than like the organizational chart of a college campus.

Before we leap to the conclusion that language and thought are represented in easily identifiable locations in the brain, it is useful to look at a large-scale summary of the literature by Vigneau *et al*. (2006). Figure 11.5 shows the results of a major meta-analysis of more than 125 brain imaging experiments, resulting in more than 700 identified regions of peak activity in the left hemisphere. The different colors represent phonology, semantics (concept-related activity), and sentence or text processes. The degree of overlap is remarkable. This is not the kind of pattern we encounter in studying sensory regions like vision, where clearly defined visual maps like V1 can be shown to map topographically on to the retina.

These facts have a strong theoretical interpretation. They suggest that much of the brain works by way of *distributed networks* of language functions, like the world-wide web. An Internet chat group may work even if the participants come from many different parts of the world. The idea of distributed brain functioning seems to support the connectionist view of the brain, as discussed in Chapter 3 (see also Neural Darwinism, Chapter 3).

By performing a statistical cluster analysis of hundreds of data sets, Vigneau *et al*. were able to suggest more specific loci, interacting in classical working memory loops (Figure 11.6). The analysis suggests three separable working memory loops, for phonological, semantic, and sentence processing. But now we are left with a puzzle that has occupied scientists at least since Pierre-Paul Broca: which figure tells us what's really happening? It is possible that the statistical analysis shows the 'true' nature of the regions in Figure 11.6. That would be a sensible interpretation if there were random jitter in the data for methodological or biological reasons. But each data point in Figure 11.5 represents the best efforts of each laboratory to ensure that there is no such random jitter. Thus we have a choice between accepting either a more localizationist account suggested by the cluster analysis, or the distributionist account suggested by Figure 11.6. It is not obvious which one is correct, and the debate continues.

Nevertheless, there is good agreement on some basic points. For example, both figures show constant interactive looping between the more sensory-related (posterior) and motor-related (anterior) parts of cortex. While the left hemisphere is usually studied because of the well-established left-side bias in most people, it is important to understand that language functions are *not* confined to the left hemisphere. There is good evidence for speech and language *input processing* on both sides – speech perception and comprehension. But for reasons that are not well understood, language *output*, the planning and control of speech, is weighted toward the left hemisphere in more than 90 percent of the population. As we will see later, the right hemisphere may even have its own way of understanding sophisticated communications like jokes, metaphors, and irony, while the left side may have a more humdrum preference for literal language (Zaidel *et al*., 2000).

We will see these ideas again as we explore how the brain supports human language and thought. Various scientists have suggested somewhat different interpretations of the very large empirical literature. We have carefully collected evidence from studies of brain damage, single-neuron recording, positron emission tomography (PET), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), electroencephalography (EEG), evoked potentials, and the like. Not all the evidence is easily reconciled, but it is useful to take a broad organizing perspective.

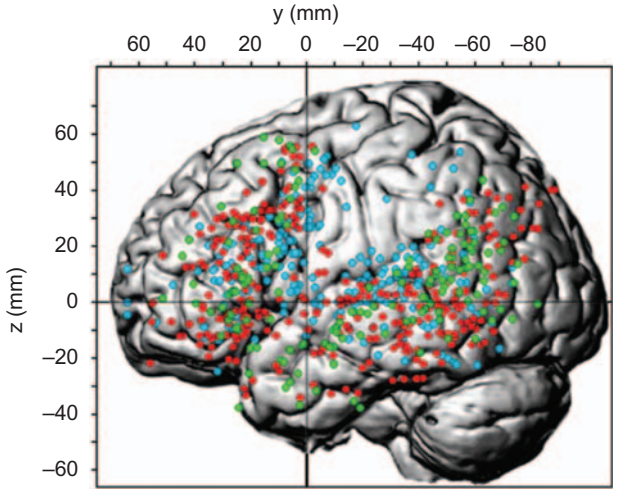


FIGURE 11.5 Widely distributed language networks may be compatible with regional specialization. A summary of more than 100 brain imaging experiments, reflecting some 730 activity peaks using fMRI and PET (Vigneau *et al*., 2006). The blue points show peaks for phonology – the sounds of speech. Red regions show peak regions for semantics, the meanings of words and phrases, and the green dots show the effects of sentences and text. The overlap and wide scatter of the three functions is striking. *Source*: Vigneau *et al*., 2006.

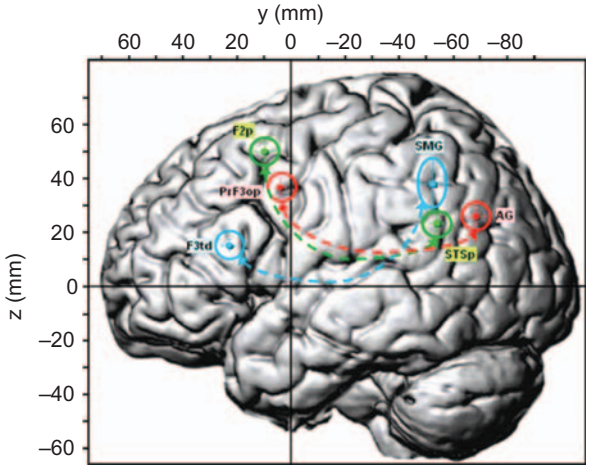


FIGURE 11.6 Working memory loops for phonology, semantics, and sentences. The wide scatter of peak activations in Figure 11.5 can be simplified by a cluster analysis, resulting in plausible centers of speech-related activity in the left hemisphere. However, such an analysis must then explain why the wide distribution of phonology, semantics, and sentence processing was found in the first place. The answers are not obvious at this time. (STSp: superior temporal sulcus, posterior; AG: angular gyrus; SMG: supramarginal gyrus; F2p: middle frontal gyrus, posterior; PrF3op: operculum of inferior frontal gyrus; F3td: inferior frontal gyrus). The word 'operculum' refers to a flap of cortical tissue that covers the hidden regions of the insula and Sylvian fissure. Frontal gyri are numbered downward (superior = F1, middle = F2, inferior = F3). *Source*: Vigneau *et al*., 2006.

For example, Hagoort (2005) suggests that we should take a larger view of what is classically called Broca's area. He proposes a division of labor as shown in Figure 11.7. Broca's area has now expanded forward to include the gray oval area, which is proposed to serve the function of *unifying* speech sounds, meaning, and syntactic relationships. This area is intended to include both memory areas of the temporal lobe, including the MTL (medial temporal lobe, which is hidden in the left viewpoint). Finally, an executive region includes the dorsolateral prefrontal cortex (DL-PFC).

As we know from the dramatic case of young children with left hemisphere surgeries, the left-side bias for language can switch to the other side if there is severe damage to the speaking hemisphere in early childhood (see Chapter 2). Lateralization of function is also found in some other species, but the reasons for it are still quite mysterious. For this topic, it is only important to understand that the wide distribution of language activity points is not limited to the left hemisphere. It expands like some vast metropolis into the non-speaking hemisphere. Anatomically, the great bridge between the hemispheres, the corpus callosum, fans out on both sides in a point-to-point fashion, so that neurons in the frontal cortex on one side sprout axons that spread across to the frontal cortex on the other side (see Chapter 5). For many functions, the two hemispheres are thoroughly integrated.

It is still true that damage to Broca's area will tend to impair speech output, while damage to Wernicke's area and neighboring regions tends to degrade speech comprehension (Figure 11.8). Historically, Broca and Wernicke were not wrong on the evidence – they just didn't have the complete story.

In Figure 11.11, we present a model for auditory language in the cortex proposed by Hickok and Poeppel (2007). Notice that the upper regions of the temporal lobe, toward the back of the Sylvian fissure, contain auditory regions that are believed to represent phonemes or possibly the 'syllabary' mentioned above. These are the sound-based representations of speech (Figure 11.11). This is a plausible model, but as mentioned, we do not yet have the spatial resolution to know whether there is a more microscopic mosaic of feature-sensitive neurons, such as exist in visual cortex.

BOX 11.2 Creole languages are produced by children in multilingual communities

Creoles are languages with simple syntactic structures that develop when speakers of several different languages are forced to communicate with one another. This can occur through immigration and invasion or when individuals are brought together from different cultures to work. The adults in such situations develop a crude pidgin, an impoverished communication system in which a limited number of nouns, verbs, and modifiers are combined with extensive gesturing. Children of the pidgin speakers learn their parents' language, but not the pidgin; instead, in addition to using their parents' language, they also create a creole for communication with one another that is based on the pidgin. All creoles share a set of common features, which are surprisingly similar to the features of fully developed languages. Thus, the children develop a much more full-fledged language than their parents in these communities.

1. The grammar is based on word order; in contrast, most human languages rely largely on inflection (agreement and derivation – see earlier discussion).
2. There are seven parts of speech: nouns, pronouns, adjectives, verbs, adverbs, articles, and conjunctions; many human languages omit one or more of these categories or add new ones.
3. Nouns are distinguished as singular, plural, or indefinite in number; many languages lack the latter category.
4. There are three particles used as auxiliary verbs to indicate whether an action is successful, unsuccessful, or repeated; many languages lack these distinctions.
5. There is a single verb conjugation system; most languages have a general rule for most verbs, but special-case rules for most of the commonly used (irregular) verbs.
6. Questions are based on intonation rather than word order; many languages use both.

Bickerton points out that, in many cases, these universal features of creoles are not present in the languages spoken by the parents of the children who created the creole. Therefore, creoles are very likely to be related to innately specified features of language.

However, even creoles do not illustrate such features directly. If all the features of creoles just listed were innate, it would be impossible to explain how any languages have any other features. Innate properties of language must be more abstract than the features found in creoles and must allow all the different forms of language that are currently found to develop. Instead of thinking of creoles as demonstrating universal features of language directly, we might better think of them as showing us what features of language develop most easily. It is possible that these features characterized human languages at an early stage of their development.

From Squire *et al*. (2003).

2.2 Language origins

People have wondered about the origins of language for thousands of years. If children grew up without language, would they invent their own? In fact, nature provides experiments a little bit like that. In some isolated communities, like small islands, adult speakers of different languages may settle in the same place. Fluent adults rarely acquire the 'accent' (phonology) or grammar of languages they learn

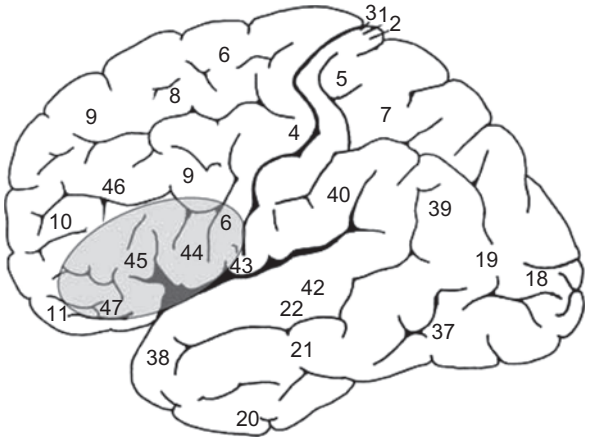


FIGURE 11.7 L-IFG: an expanded concept of Broca's area. The left inferior frontal gyrus (L-IFG) is a more accurate label for the broad area involved in speech planning and production. Hagoort (2005) also suggests that L-IFG is a 'convergence zone' for speech, i.e. it is a place where the different features of spoken language are unified into an integrated plan before being sent to the motor map. *Source*: Hagoort, 2005.

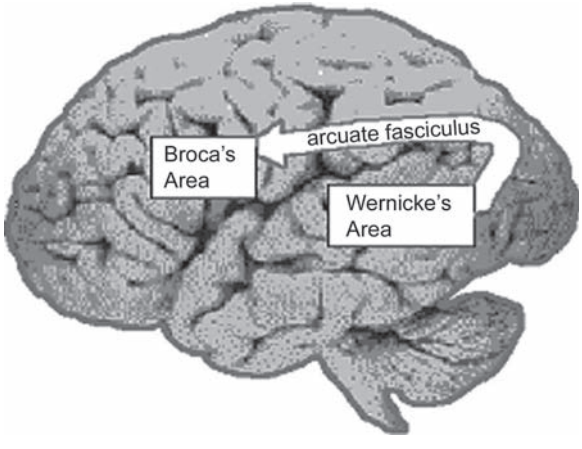


FIGURE 11.8 Wernicke-Geschwind model. The best-known neurologically based model of the language regions is due to Geschwind (1979). While the Wernicke-Geschwind model continues to be widely studied, the advent of neuroimaging methods has led to a wave of new evidence. *Source*: Weems and Reggia, 2006.

after puberty. Instead, they tend to speak a 'broken' version of the new language, one that is good enough to communicate with adults from other parts of the world, but generally without the fluency and expressive richness of their original languages. Children in such bicultural communities do a very interesting thing: they may develop a language of their own, now called a 'creole' because they were first studied in the Creole communities of the Caribbean Islands (Box 11.2; Bickerton, 1984, 1990).

FRONTIERS OF COGNITIVE NEUROSCIENCE

How spoken sentences are processed in the brain

FIGURE 11.9 Angela D. Friederici, PhD, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany.

We communicate mostly by spoken language. Spoken sentences contain not only semantic and syntactic information, conveying the meaning of words and their grammatical relationships (who is doing what to whom), but, moreover, prosodic information – the melody and rhythm of language. Prosody can provide information signalling the boundaries of syntactic phrases, and it can also tell us about the emotional tone modulating meanings. Neuroimaging indicates that semantic and syntactic processes are supported by neural networks in the left hemisphere, comprising inferior frontal regions (Broca's area and more anterior parts) and superior and middle temporal regions (largely Wernicke's area) (Friederici, 2002; Hickok & Poeppel, 2007). The functional network for syntax includes Broca's area (Stromswold *et al*., 1996) and the most posterior portion of the superior temporal gyrus and sulcus (Bornkessel *et al*., 2004); semantics recruits brain regions anterior to Broca's area in the inferior frontal gyrus (Thompson-Schill *et al*., 1997) and portions of the middle and superior temporal gyrus (Demonet *et al*., 1994). For syntactically complex sentences, we see activation in the network that connects Broca's area and the posterior superior temporal gyrus (Friederici *et al*., 2006a). Recent work indicates that within this fronto-temporal network Broca's area serves the function of processing syntactic hierarchies independent of the sequence's meaning (Friederici *et al*., 2006b; Makuuchi *et al*., 2009). The posterior temporal region comes into play when processing syntactically complex meaningful sentences (Bornkessel *et al*., 2004; Friederici *et al*., 2009). The last finding suggests that the posterior temporal cortex helps to integrate meaning and syntax in sentence comprehension.

Prosodic information – the melody of language – is processed in the right hemisphere, especially the superior temporal and inferior frontal regions (Meyer *et al*., 2002). Event-related brain potentials (ERPs) indicate that intonational phrase boundaries can guide or mislead our ability to parse sentence syntax when listening to sentences (Steinhauer *et al*., 1999). For example, the two sentences: (a) S*ince John always jogs two miles this seems like a short distance to him* and (b) *Since John always jogs two miles seems like a short distance to him* are clearly syntactically different. If you read them carefully you'll see that they are both meaningful, normal sentences – they just have a different intonational boundary. In sentence (a) we can express the end of a phrase after 'miles'; in (b) we change our intonation after 'jogs'. An intonational break after 'jogs' in sentence (a) would mislead our ability to parse the syntax of the sentence.

This suggests a strong interaction between the left hemisphere's syntactic processing, and the right hemisphere's prosodic processing. That interhemispheric interplay is guaranteed by fiber bundles connecting the two hemispheres; that is, the corpus callosum. ERP data from patients with lesions in the posterior third of the corpus callosum indicate that this brain structure is crucial for the interplay of syntactic and prosodic information (Friederici *et al*., 2007). It allows the two information types to interact early on, to help speed our understanding of spoken sentences (Eckstein *et al*., 2006).

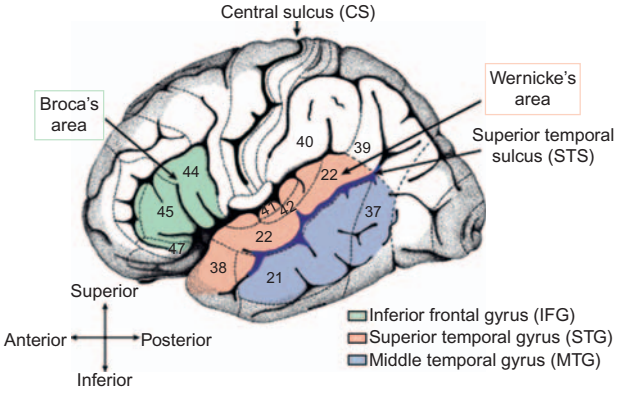


FIGURE 11.10 A schematic view of the language regions in the left hemisphere, with major relevant gyri and sulci. Numbers indicate language-related Brodmann areas (BA), defined on the basis of their microscopic cellular characteristics (Brodmann, 1909). The classical language areas are Broca's area (BA 44 and 45) and Wernicke's area (BA 22). The words 'superior' or 'inferior' refer to the position of a gyrus within a lobe (e.g. superior temporal gyrus) or within a Brodmann area (e.g. the superior BA 44). The terms 'anterior' or 'posterior' indicate the position within a gyrus (e.g. the posterior superior temporal gyrus). *Source*: Friederici.

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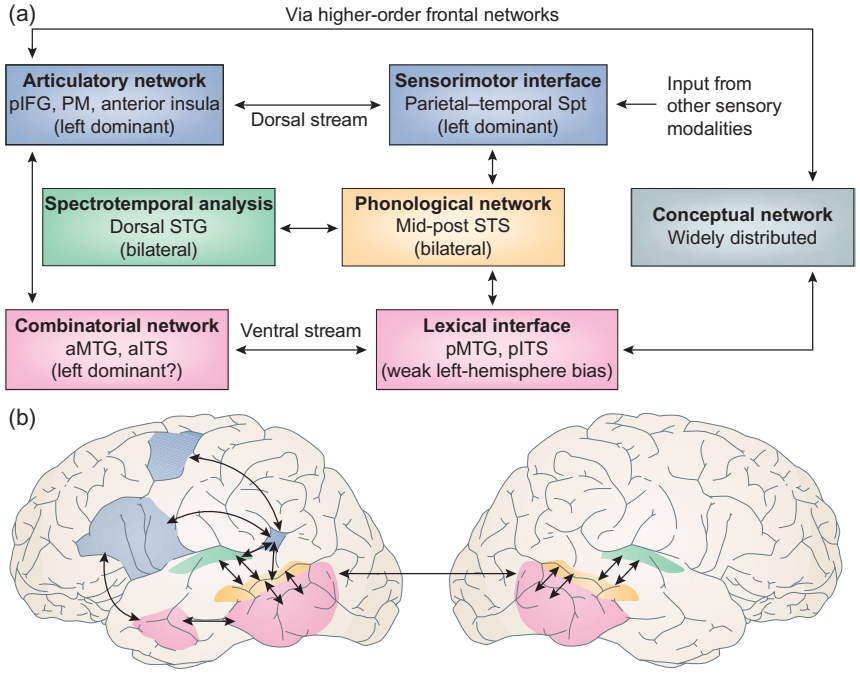


FIGURE 11.11 Hickok-Poeppel model of auditory language. Upper panel shows a schematic for the model of auditory language processing proposed by Hickok and Poeppel (2004). Lower panel shows brain regions proposed to reflect stages of the model. Note that early speech perceptual systems for mapping the acoustic-phonetic information in sounds onto meaning are proposed to be mediated bilaterally in left and right hemispheres while later processes are proposed to be mediated by left hemisphere regions. *Source*: Adapted with permission from Hickok and Poeppel, 2007.

2.3 Speech versus language

Scholars often make a distinction between speech and language, in part because of the striking plasticity of the human brain in learning different input and output modalities. Right now you are using your eyes and perhaps your hands, to take notes. You have learned to read and write or type with quite remarkable facility. You could also learn sign language, Braille, and paralinguistic symbol systems like mathematics, logic, and computer programming. Thus, the purely vocal and auditory nature of speech seems to be unnecessary.

However, a hard-and-fast distinction between speech and language is not justified. Human brains are pre-adapted to acquire auditory and vocal speech. The great majority of children learn spoken language in the first years of life, but reading and writing come later and have a lower rate of success. The fact that we can exercise remarkable linguistic flexibility, given the need and the opportunity, does not falsify the biological primacy of spoken language.

3.0 THE SOUNDS OF SPOKEN LANGUAGE

Chapter 7 discussed the auditory nature of speech, consisting of fast-expanding three-dimensional bubbles of high and low air pressure waves, which set the delicate membranes of the inner ear into vibrating motion. We can also look at speech from a vocal *output* point of view.

The human vocal tract is basically a tube, with two flexible flaps just above the lungs and its diaphragm muscles, which together create air pressure when we breathe out (Figure 11.12). The vocal tract is therefore much like a reed horn like a saxophone, with the reed vibrating at the top of the tube. The vocal flaps can vibrate faster or slower, producing higher- or lower-pitched sounds. We produce consonants by closing the entire vocal tube at one of several places. In English we use the lips at the very front (/b//p/ /m/), the tongue against the palate in the back or middle (/g//k//ng//r/), and the teeth in the front (/th//the//s//z//v//w/). However, stopping the flow of air completely produces no sound at all, so that it is the fast *transitions* between closing and opening of the air flow that produces the so-called stop consonants (/b//p//t//d//k/g/). Other languages shape the air flow in somewhat different ways, but the physical principles of sound production are the same.

Vocal vibrations echo through the head and body, triggering vibrations in all the cavities in our head and torso, so that by holding one's nose, for example, one can change the quality of the voice. Those vibrating air-filled body cavities also allow us to tell the difference between individual voices. Children's voices sound higher than adults' simply because they have smaller vibrating cavities.

Just as closing the vocal tube creates consonants, shaping the vocal cavity with the mouth open produces different vowels. Singing is closely related to speaking: it is just stretching the length of vowels and tuning them to a specific pitch using the vocal cords. But even ordinary speech has a kind of melodic phrasing called *intonation contours*. In English, a question intonation tends to raise the pitch of the last few syllables of a spoken phrase. A great range of emotional qualities is conveyed by the intonational melodies of speech.

Even the rhythm of music has a close analogue in vocal stress patterns, as used in poetry and rap music, for example. Thus, singing and speech intonation, rhythm, and vocal gestures can be viewed as using the same voice instrument in somewhat different ways.

In sum, humans can shape the vocal tract in a great variety of ways, a rare (but not unique) adaptation among animal species.

Until the invention of typewriting, speaking was the fastest moving and most precise skill that most people ever acquired. As Chapter 7 points out, the difference between the syllable /pa/ and /ba/ involves only a few tens of milliseconds between the onset of vocal vibrations and the opening of the lips. In the case of /pa/ the lips open slightly before voicing begins, while for /ba/, voice onset starts just before the lips open up. Because we are skilled readers and writers, we tend to believe intuitively that language is made up of sequences of letters, but that is a misunderstanding. Spoken language involves a series of articulatory gestures, which shape the moment-to-moment frequency distribution of air vibrations emanating from our vocal tract. While we can *see* isolated visual letters (as on this page), there is no such thing as an isolated vocal consonant. We cannot pronounce /k/ without making a following sound, even if it is just a long /hhhh/, simply because the tube needs both to *close and open* to produce any sound. For that reason, the physics of sound suggests that simple syllables (like /ba/ and /pa/) and isolated vowels may

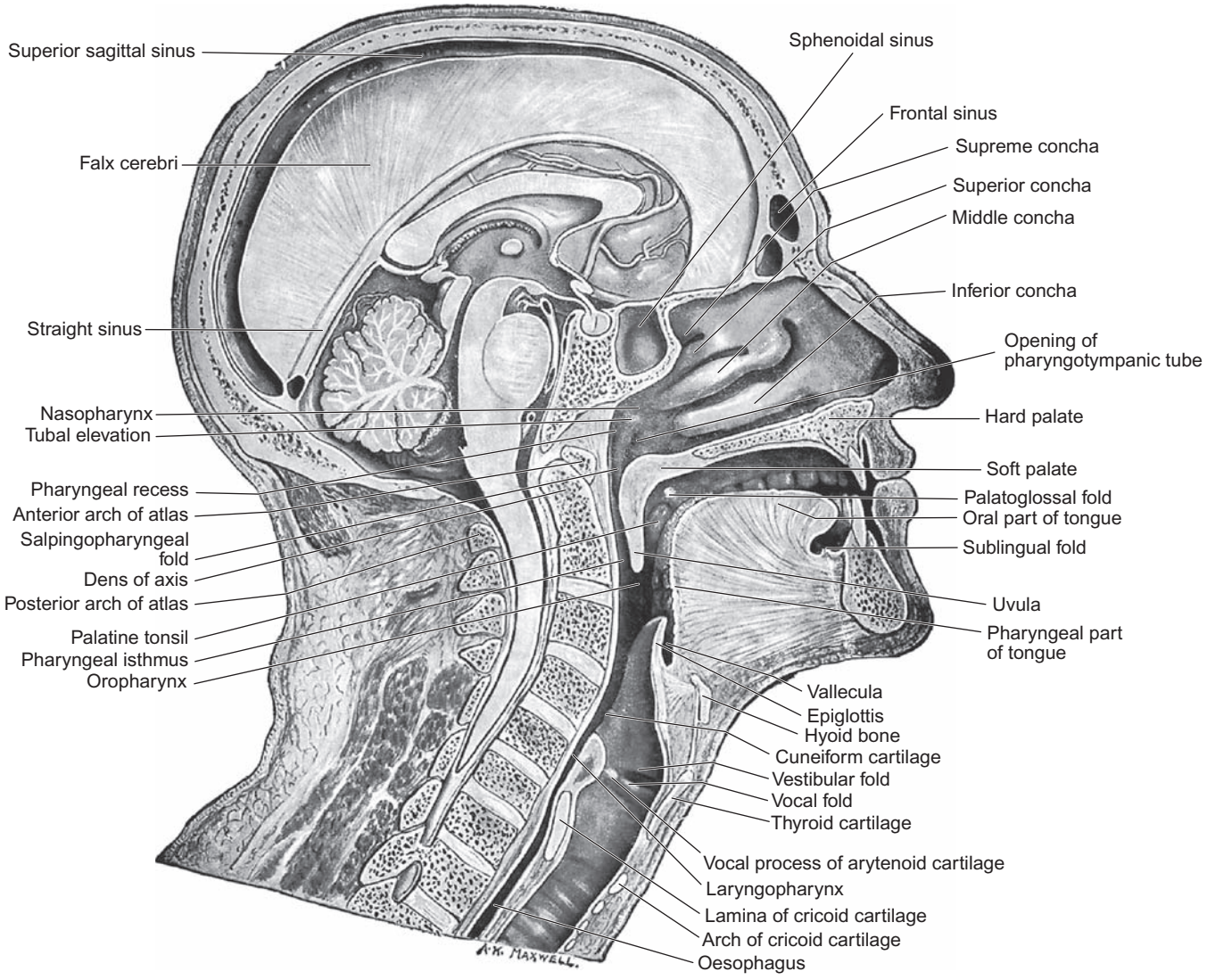


FIGURE 11.12 The human vocal tract makes use of pre-existing mechanisms of breath control, mouth, tongue, glottis, and larynx inherited from ancestral species. The vocal tract is a tube with a source of tuned vibrations in the vocal cords, two flaps of tissue in the larynx. The quality of vocal sounds results from vibratory resonance with the movable tissues and air pockets throughout the head and torso. While consonants involve restriction of closing of the air tube, vowels are mostly shaped by moving the tongue and lips to shape the oral cavity. This has the effect of changing the resonant frequencies or formants of the vocal tract. Thus vowels and consonant-vowel pairs are the minimal physical units of speech production (if one considers hissing sounds like /h//th//tha//s/ and so on to be vowel-like). *Source*: Standring, 2005.

be the simplest elements of speech. For that reason some theorists suggest that humans make use of a syllabary – not just an alphabet of phonemes, but a larger set of speech gestures of vowels and consonant-vowel combinations (Levelt and Wheeldon, 1994). A syllable alphabet would have to be larger than a set of phonemes, but it would reflect the way we produce speech sounds.

It follows from these points that the phonemes of human language are abstract percepts, much as visual objects are. Our eyes don't see trees – rather, they receive retinal projections of light and dark that are interpreted by the cortex as three-dimensional trees at a certain distance from the eyes. Similarly, phonemes are *abstract* categories of sounds, which are acoustically quite different depending upon their neighboring speech gestures. When speakers say /ba/ versus /bee/, the acoustical information for the lip-opening that produces the consonant /b/ is quite different in the two cases. In the case of /bee/ there is a fast-*rising* transition to signal the consonant, while for /ba/ there is a fast-*dropping* transition (see Chapter 7). Yet we perceive the consonant /b/ to be the same in both

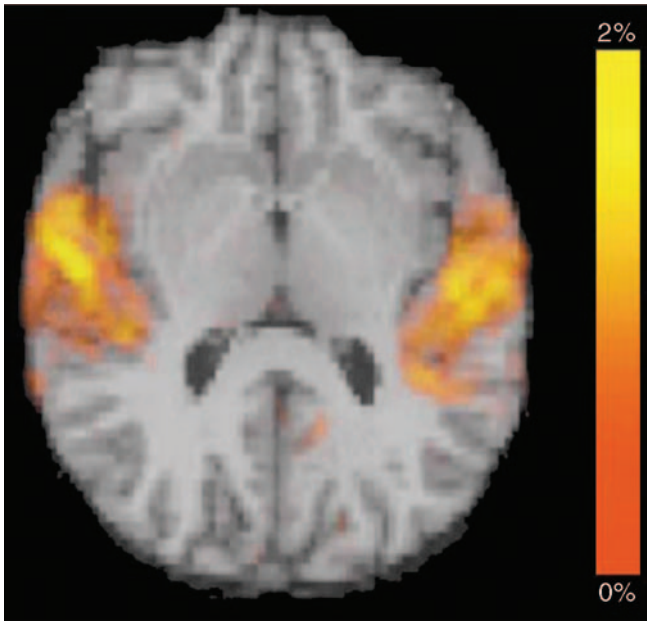


FIGURE 11.13 Auditory cortex shows local activity to different speech-like stimuli. Recent research shows finer parcellation of the auditory and speech perception regions. With the development of more refined imaging tools, it is possible that localized arrays of speech feature-sensitive neurons will be identified, much as has happened in the visual cortex. *Source*: Langers *et al*., 2003.

cases. This is typical for human languages, which tend to have about forty *abstract* phonemes, which stand for the much larger set of physical sounds that actually reach our ears. Abstract phoneme perception appears to be species-specific.

Are phonemes reflected in neat fields of feature-sensitive neurons in the cortex? We do not know the answer. In the case of vision, feature-sensitive cells that respond to color, line orientation, and the like, were first discovered in the macaque monkey, using single-cell recording. Such experiments are not done on humans, and of course macaques are not biologically adapted for speech perception. For that reason the answers still await better brain imaging methods (but see Figures 11.13 and 11.14 for recent studies investigating brain processes for speech and speech like sounds and gestures). Reports of high-resolution fMRI studies of auditory cortex in the macaque were published even as this book was going to press (Petkov *et al*., 2006). In the next several years we may find out if there are feature-sensitive fields of auditory neurons in the cortex. Because the brain tends to do things similarly for similar functions in the cortex, it seems like a reasonable prediction. But direct evidence is simply not available.

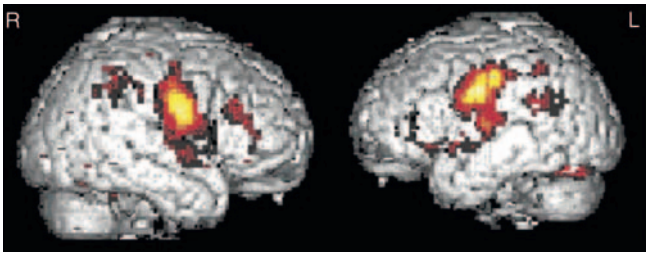


FIGURE 11.14 Extending the tongue without making a sound. Even without making a sound, horizontally extending the tongue shows marked activity in the 'language' regions of both hemispheres. As this shows, the tongue and mouth are very well represented in motor cortex, unlike, for example, regions of the back. Motor cortex over-represents more important regions of motor control, and under-represents less important ones. *Source*: Dogil *et al*., 2002.

4.0 PLANNING AND PRODUCING SPEECH

Output from the language areas of cortex is at least as complex and adaptive as speech perception and comprehension. Figure 11.15 shows pathways between speech perception and production. Figure 11.16 shows a current model of the output flow, beginning with the conceptual level. Grammatical encoding of sentences is believed to involve lemmas, much like formulas for translating semantics into the morphemes and phonemes that govern vocal movements. It is important to understand again that these linguistic units are abstract, in the sense that any given phoneme, for example, can be articulated in more than one way, depending upon the neighboring phonemes. The vocal tract is a physical system, and it takes considerable time for the tongue, for example, to travel between the teeth (for shaping the consonant /th/) and the soft palate at the back of the mouth to make a /g/ sound. As a result, there is a fair amount of 'sloppiness' in the acoustical signal that is produced, because of the smearing of speech gestures. In English, for example, the word 'tan' will foreshadow the final /n/ even during the time when the /ae/ is being pronounced. The /ae/ is therefore nasalized or 'co-articulated'. Thus, the actual sounds of speech changes, even though the abstract phoneme is believed to be represented the same way, whether we have the /ae/ in 'act' or in 'tan'. If you listen carefully, you will be able to hear the difference.

Notice that this situation parallels the case of vision. In the visual cortex, area V1 mirrors the output of the retina. It is very detailed, with small receptive fields and very high optical resolution. Even though later

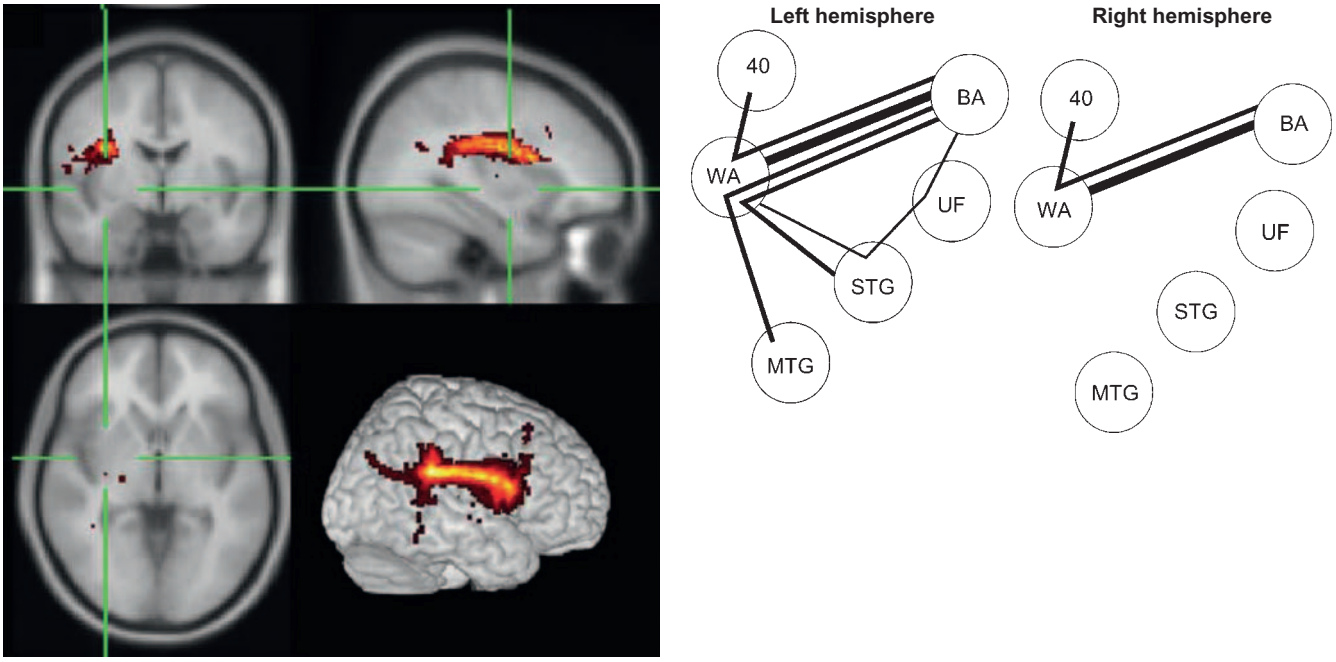


FIGURE 11.15 Pathways between speaking and hearing. The results of a tractography study of the connections between production and perception regions. The tractographic display (above) shows the classical arcuate fasciculus running between Broca's and Wernicke's areas, although an additional pathway has been reported as well. The lower two figures show mathematical connection weights for the left and right hemispheres, respectively. (BA: Broca's area; WA: Wernicke's area; UF: uncinate fasciculus; STG: superior temporal gyrus; MTG: middle temporal gyrus.) *Source*: Parker *et al.*, 2005.

visual areas are also visuotopic maps, they are much less detailed and much more abstract in representing features of the visual input like color, object identity, and the like. The idea that the visual system becomes more abstract as we look upstream is therefore well justified by the evidence. Speech may be similar in that respect, although our brain evidence is far less complete.

Notice also that the cortex is not the only control region for speaking. Actions that are initiated voluntarily from frontal cortex also enlist regions of the basal ganglia and cerebellum. Traditionally, it has been believed that basal ganglia are involved in the automatic aspects of action control, such as the specific pronunciation of /r/ sounds compared to /l/ sounds, a distinction that is very difficult for native Japanese speakers, for example. English speakers have comparable difficulties in controlling the French sound /u/ versus /oo/. These highly overpracticed speech sounds are not completely controlled by the cortex. In addition, the cerebellum is traditionally believed to be needed for fine motor control.

However, recent brain imaging evidence implicates both the cerebellum and basal ganglia in purely cognitive aspects of brain activities, including working memory and some types of associative learning (Figure 11.17).

While language areas of the cortex have been known since the 19th century, even the exact functions of Broca's and Wernicke's area are still debated (see Chapter 1). It isn't that Broca and Wernicke were wrong in their proposals about speech production and comprehension. Rather, as our observations become more and more precise, we are finding more functions for the classical language regions of the left hemisphere, and speech-related functions outside their traditional boundaries. Our understanding is constantly being revised. We are, in effect, exploring a new planet, and as our space probe comes closer and closer, we need to chart a much more detailed and surprising geography of this novel world.

5.0 EVOLUTIONARY ASPECTS OF SPEAKING AND LISTENING

Our highly specialized vocal apparatus is attuned to producing spoken language. It evolved from the nonlinguistic vocal organs of ancestral species. These, in

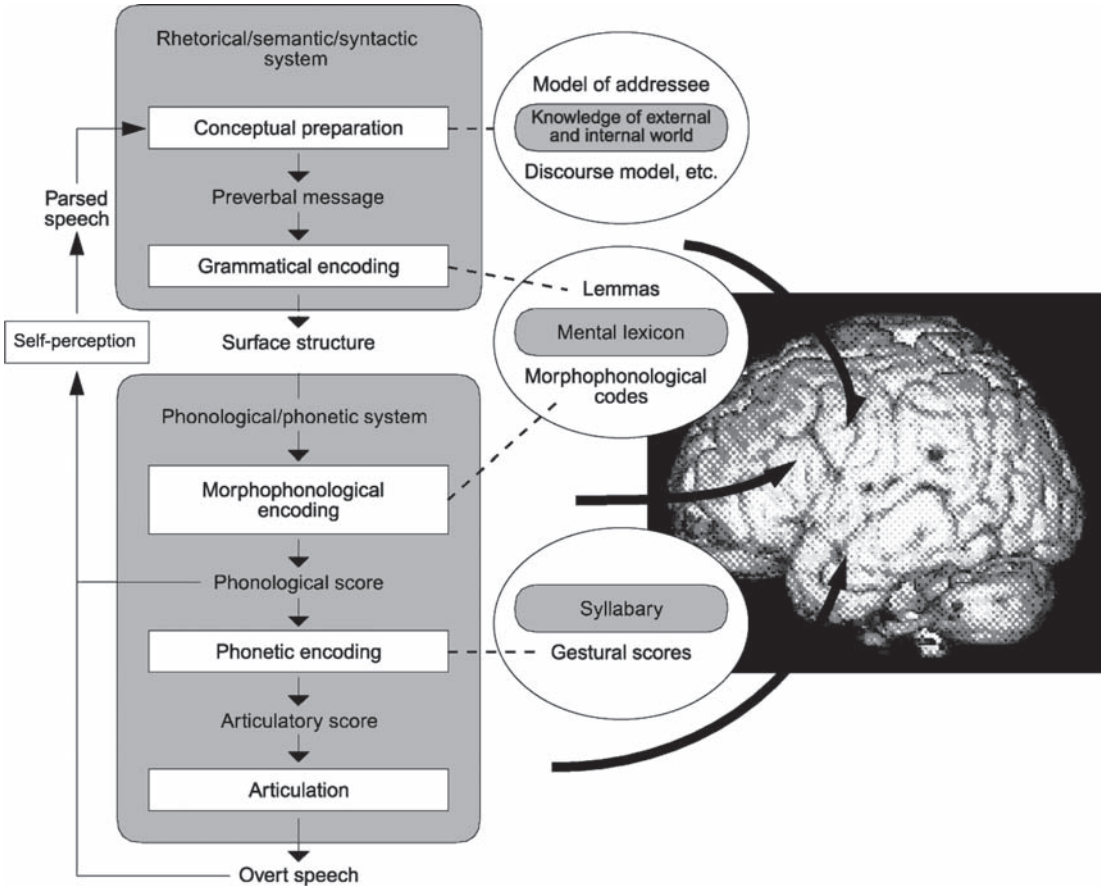


FIGURE 11.16 Producing speech: from meaning to movements. A model of the production of speech. Compare to Figure 11.1. *Source*: Dogil *et al.*, 2002.

turn, build upon a breathing apparatus that we share with other land-dwelling creatures, as well as neuromuscular control of chewing and swallowing. For example, tree-dwelling young gibbons in the wild sound very much like human children at play. However, soon after birth human babies begin to babble, experimenting with syllables that are quite different from non-linguistic sounds (Schirmer and Kotz, 2006).

Anatomically, vocalization involves a dual-control system, like breathing and emotional facial expressions (Chapter 2). In socially provocative situations, vocal sounds can be produced with minimal executive control from the lateral prefrontal cortex, ranging from making cooing sounds to a baby, to crying out of sadness, shouting with anger, or groaning with distress. Figure 11.18 shows the dual control of vocalization schematically. As you can tell, it is not a simple system, having evolved over many millions of years.

In this chapter, we are concerned with the right side of the diagram, the cortical control of speech beginning with prefrontal cortex and Broca's area (broadly defined), while on the input side we are looking at speech perception and comprehension.

Cortical regions for speech are closely associated with audition (for sensory input) and with mouth and vocal tract representation (on the output side). The classical Broca's and Wernicke's areas are adjacent to cortical regions for vocal production and sound perception, respectively (Figure 11.19). Figure 11.20 shows the mouth and vocal region of the motor homunculus, immediately adjacent to Broca's area. Direct stimulation of the motor map results in muscular movements, but stimulation of premotor regions such as BA 6 results in reports of 'urges to move' the corresponding part of the body. Motor map stimulation is perceived as externally controlled by the physician, not by the patient. Broca's area may be considered premotor cortex for speech, i.e. a cortical region for the 'intention to speak'. When Broca's area is stimulated in a conscious patient, it appears to block the intention to speak (Quinones-Hinojosa *et al.*, 2003).

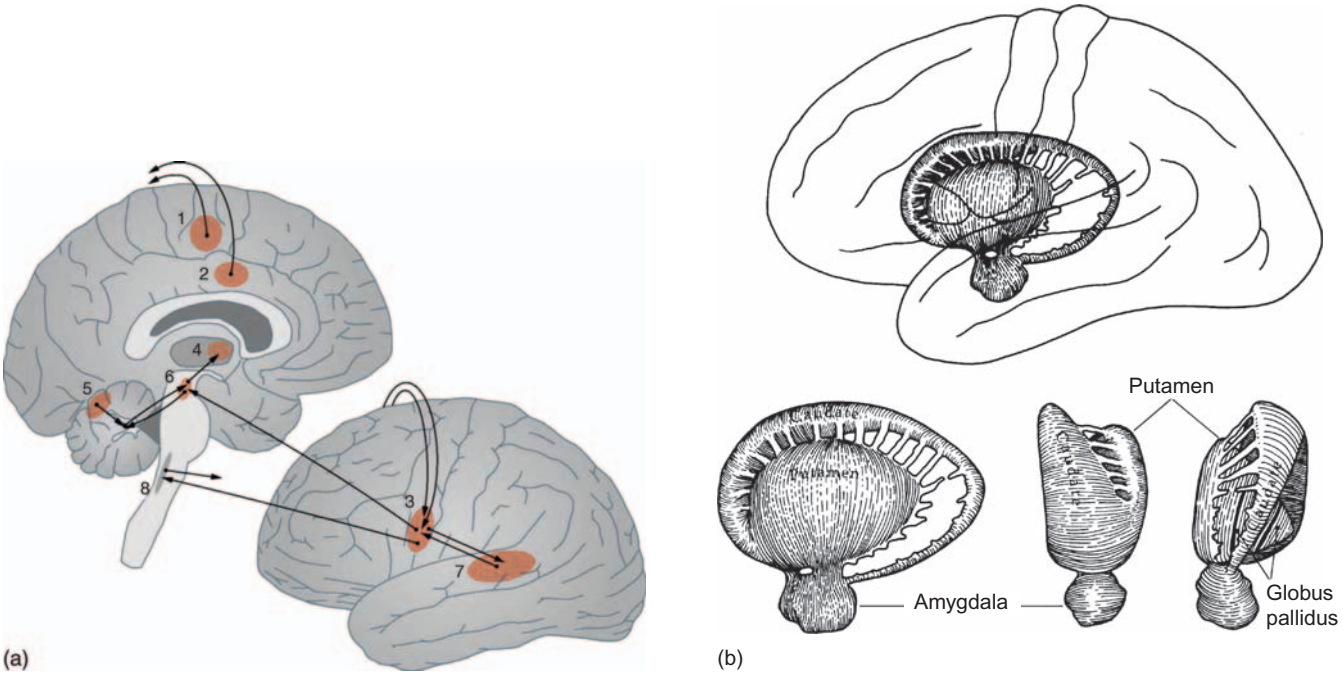


FIGURE 11.17 (a) A neural network for speech production: the supplementary motor area (1) and the cingulated motor area (2) are connected with the primary motor cortex (3). Subcortical activation is in the thalamus (4), the basal ganglia (not shown), the red nucleus (6), and the cerebellum (5). Additionally, the posterior temporal gyrus in both hemispheres is activated in speech production (7). In the brainstem, areas such as the nucleus hypoglossus (8) are innervated during speech production. Cortical regions work with the basal ganglia, thalamus, and cerebellum in speech control. Subcortical satellite regions like the basal ganglia are involved in sequential behaviors like speaking. In addition, the cerebellum and thalamic nuclei (not shown) play an important role. *Sources*: *Left*: Soros *et al*., 2006; *right*: Angerine, 2002.

As more has been learned about the cortical aspects of speech and language, the production and perception regions have expanded and also become more finely fragmented into specialized areas. Additional functions have also been discovered for the classical Broca's and Wernicke's areas, as in the case of the 'mirror neurons' discussed in Chapter 14. Speech perception (but not production) also appears to recruit the non-speaking hemisphere (the right hemisphere in most people), even though speech planning and production is typically limited to the left side.

6.0 WORDS AND MEANINGS

English is a member of the Indo-European language family. This family includes Persian and a number of languages spoken on the Indian subcontinent. Other language families make quite different choices with respect to such basic-seeming units as words. Finnish and Turkic languages are called 'agglutinative', because they string morphemes into long utterances, like the unusually long English word 'antidisestablishmentarianism'. Such long strings of morphemes are normal in agglutinative languages. Tonal languages like Chinese and Tibetan take the opposite approach, compounding sentences from typically short words, modulated by a rich melodic shaping of each syllable, so that a word like 'Chang' can mean quite different things depending on its tonal contour. However, all languages have lexical units of some kind – utterances of one or more syllables that refer to meaning categories or to relations between categories.

Figure 11.21 shows a current model of how the brain may translate different linguistics codes from one to the next. As Figure 11.1 showed, language may be viewed as a double hierarchy, going from sound to meaning on the input side, and from meaning to vocal gestures in output. But we can repeat a nonsense syllable like 'fronk' even though it has no particular meaning, and Figure 11.15 suggests that such recoding from sound to speaking may occur in the inferior parietal cortex. Broca's area was traditionally thought to serve the translation from thought to speech articulation, the current favored term is the left inferior frontal gyrus

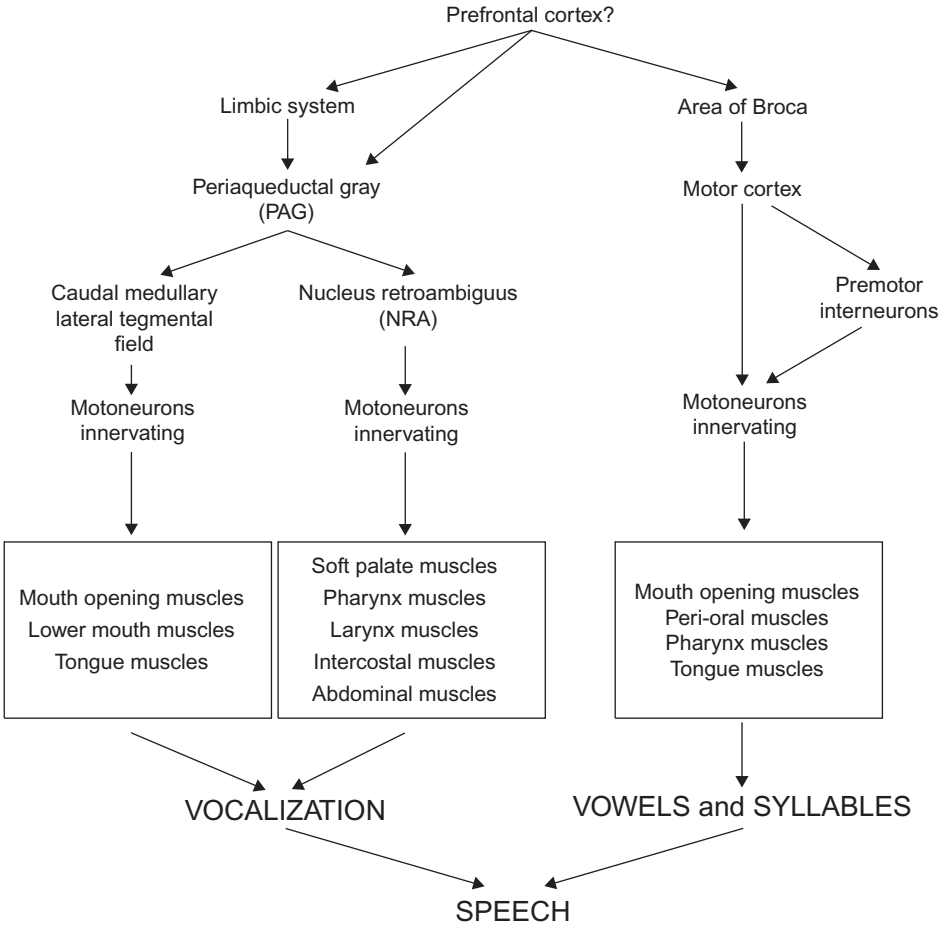


FIGURE 11.18 Speaking may have evolved from socially evoked sound production. Vocalization has a dual-control pathway, much like breathing, facial expressions, eye movements, and other motor systems. The left branch is sometimes called the emotional motor path. Originating in prefrontal cortex, it follows a classic mammalian route for vocalization including the limbic system and peri-aqueductal gray (PAG). The PAG plays a major role in distress vocalizations when rat pups and mothers are separated. Like the emotional motor path, the right-hand branch begins in prefrontal cortex, and then follows the better-known steps from Broca's area to motor cortex and thence to the cranial nerves for vocal control. Both pathways also receive input from basal ganglia and cerebellum. The right-hand pathway is under greater voluntary control. *Source*: Holstege *et al.*, 2004.

(L-IFG), because wider regions of the left hemisphere are thought to be involved. The older term 'Wernicke's area' for speech comprehension is now called the TPO junction (for temporal-parietal-occipital). This location makes sense, because we know that the temporal lobe is involved in memory-based concepts, including those abstracted from visual objects, like the differences between animate and inanimate figures, for tools and instruments, and for parts of the body. As Chapters 9 and 10 pointed out, it may be that these very specific semantic regions serve to index larger classes of words and concepts, rather than being a localized semantic field.

6.1 A cultural treasury of words and ideas

Language is used to communicate meanings. While phonemes are defined as minimal speech units that make a *difference* in meaning, words refer to things, which phonemes do not. Words are the basic building blocks of meaning. However, sentences, and particularly *propositions* built out of sentences can be taken as basic 'meaning formulae', analogous to mathematical formulae. We think and communicate in sentences. Many communications are of course elliptical, i.e. they abbreviate a whole thought into a few words. Nevertheless, they express a semantic proposition of some kind.

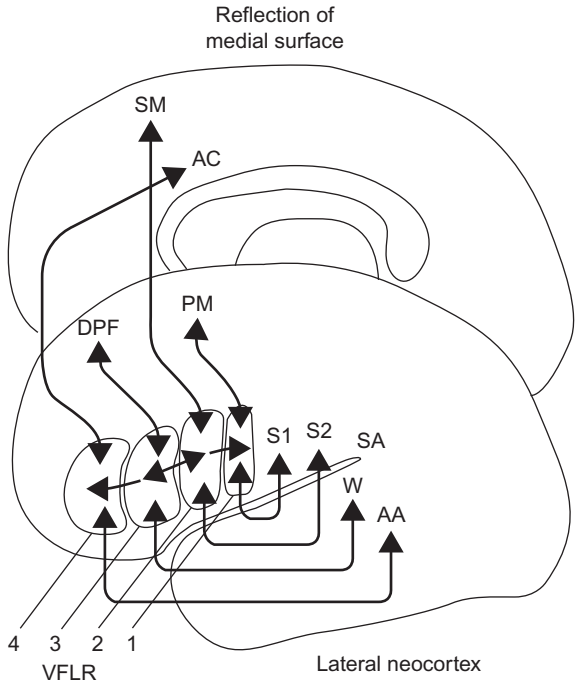


FIGURE 11.19 Speech production and perception loops constantly. Speech production and perception regions of the cortex are constantly exchanging information, both directly via subcortical connections, and indirectly, as we hear the sound of our own vocal apparatus. As pointed out in Chapter 2, there is good evidence that most people spend most of the day talking to themselves cortically. Indeed, studies of sleep stages seem to show that inner speech continues during sleep and dreaming. *Source*: Dogil *et al.*, 2002.

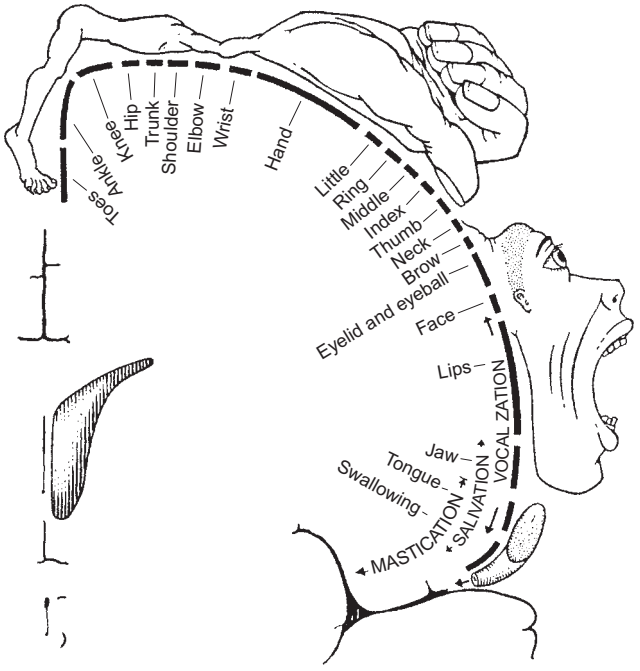


FIGURE 11.20 In the motor homunculus (BA 5), muscular control of the mouth, jaw, tongue, vocal cords, as well as actions like chewing and swallowing reside next to Broca's area for the control of speaking (BA 6, 44, and 45). The 'motor homunculus' was first discovered by Wilder Penfield using electrical stimulation of motor cortex in awake patients during exploratory neurosurgery (Penfield and Roberts, 1959). Notice that mastication, vocalization, and swallowing are marked next to the mouth region of the homunculus. *Source*: Standring, 2005.

As Chapter 10 suggested, the words of natural language are an immense legacy of useful chunks of meaning, developed over centuries. Indeed, in many cases we can trace word origins over more than a thousand years. A particularly nice example is the word 'quality' derived from the Latin translation (by Cicero) of the ancient Greek expression 'po io tes', or 'what is it-ness'. Cicero apparently encountered it in a Socratic dialogue. Before his invented word *qualitas* became popular, European languages had no way to refer to the 'what is it-ness' of a sound, of a taste, or any other class of events. We can always use longer phrases for the ideas for which we do not have single words, but single words allow us to treat concepts as single chunks in our very limited working memory space. Thus, inventing new and useful words is a real contribution to our capacity to understand the world.

Science is hard to imagine without a word like 'quality'. Yet it took a certain realization at a certain point in intellectual history, more than twenty centuries ago, to chunk the concept of 'quality' in a way that we can use as an abstract noun. Probably all modern

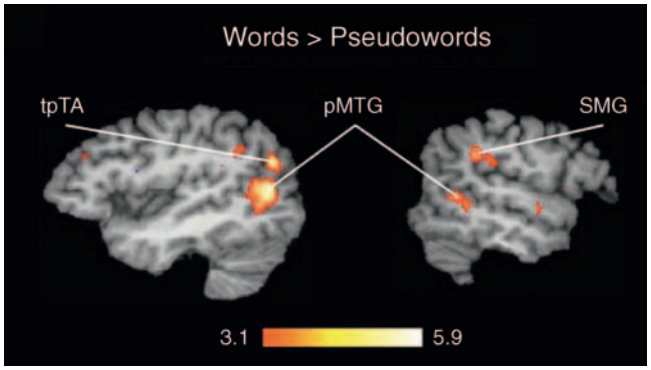


FIGURE 11.21 Brain activations for meaningful versus meaningless words. Words are not just sequences of phonemes. Although the brain basis of word meaning continues to be mysterious (presumably because word meanings are part of long-term memory; see Chapter 9), meaningful words activate distinct regions of language-related cortex, when compared to nonsense words. In this study, three areas appeared in the comparison, the temporoparietal transition area (tpTA), the posterior part of the medial temporal gyrus (pMTG), and the supramarginal gyrus (SMG). *Source*: Friederici and Kotz, 2003.

languages have some term for 'quality' today, because we can no longer think easily without it. Since modern languages have tens of thousands of words, with more being produced every day, we must multiply Cicero's invention by tens of thousands of other invented words to get some sense of the body of knowledge that is passed down to each new native speaker.

Roget's Thesaurus, first compiled by Peter Mark Roget (1779–1869), is one historic effort to classify the words of a natural language into its semantic categories, so that one can find a word by starting with a concept. In a thesaurus, words with similar meanings are clustered together, giving us a kind of semantic treasury of standard ideas; indeed the word 'thesaurus' means 'treasure'. Modern efforts along those lines use computational methods, but characterizing our knowledge of basic concepts is still an awesome enterprise. George A. Miller's WordNet system at Princeton University is one effort along those lines (http://wordnet.princeton.edu/), an online lexical reference system. Over a period of years, it has classified more than 200,000 word-meaning pairs in English. Parallel efforts have been undertaken for other languages. By the WordNet count, English has some 128,000 single-meaning words, and about 80,000 words with multiple meanings. However, this estimate does not include words with multiple syntactic roles, like 'book', which is both a noun and a verb (as in 'booking the arrested person'). 'Book' also can be adjectival (as in book-learning, book-binding, a bookish person, a book-reader, and so on.).

Thus, the words and meanings that we know as skilled speakers of human language are enormous. The *Oxford English Dictionary* (OED) is another massive effort along similar lines, tracing the history of standard English words to their written origins. Obviously, however, the real origins of words are lost in time, since language is basically a spoken medium, which only turned into a standardized printed body of knowledge long after the invention of writing, two or three millennia ago. Nevertheless, the OED gives us some sense of the sheer size of the human lexicon of words and concepts.

6.2 Recognizing synonyms

Gitelman *et al*. (2005) made a state-of-the-art effort to specify language areas using the identical cognitive task with the same group of subjects, looking at orthography (spelling), semantics, and phonology in the same experimental session. (Syntax involves word sequencing, and is therefore left until later.) Subjects were shown word pairs as in Figure 11.22, and asked to respond either 'same' or 'different'. In the case of 'rain' versus 'reign', they were to say if the words were homophones (HOM), i.e. words with different spelling but the same pronunciation. In the case of 'boat' versus 'ship', they were to identify synonyms (SYN), different words with the same meaning. In the case of 'aunt' versus 'tuna', they were to identify anagrams (scrambled letters, ANA); and in the control condition they were simply identifying whether two sets of four consonants were the same or different. The control condition allows common activity due to reading, visual stimulation, and the like to be subtracted from the other conditions. fMRI was recorded during stimulus exposure in each same-different trial. Comparisons were made within individuals to minimize inter-individual differences. Word stimuli were carefully selected for equal numbers of nouns and verbs in comparison conditions, while other variables like word frequency were controlled statistically.

Figure 11.23 shows the results for the HOM and SYN conditions.

6.3 Current evidence about words and their meanings is fragmentary

As Chapter 10 points out, we only know a few brain locations that are differentially sensitive to specific meanings, such as tools, animate versus inanimate objects, and the like. The function of those locations is still unclear. As Moscovitch (1992) has suggested, they could function as *indices* to a wide network of meaning-related connectivities in the neocortex. It is always possible that advances in brain recording methods will reveal a thesaurus-like array of neuronal patches, corresponding to semantic categories

	Phonologic (HOM)	*Semantic* (SYN)	*Orthographic* (ANA)	*Control* (C)
Match *(response)*	Rain Reign	Boat Ship	Aunt Tuna	Fplk Fplk
Non-Match *(no response)*	Axe Ask	Key Lock	Horse Short	Gkjs Gskt

FIGURE 11.22 Sample stimuli from the Gitelman *et al*. (2005) study. The experimental conditions are shown and include phonologic (homophone, HOM), semantic (synonym, SYN), and orthographic (anagram, ANA) contrasts in a match and a non-match condition. *Source*: Gitelman *et al*., 2005.

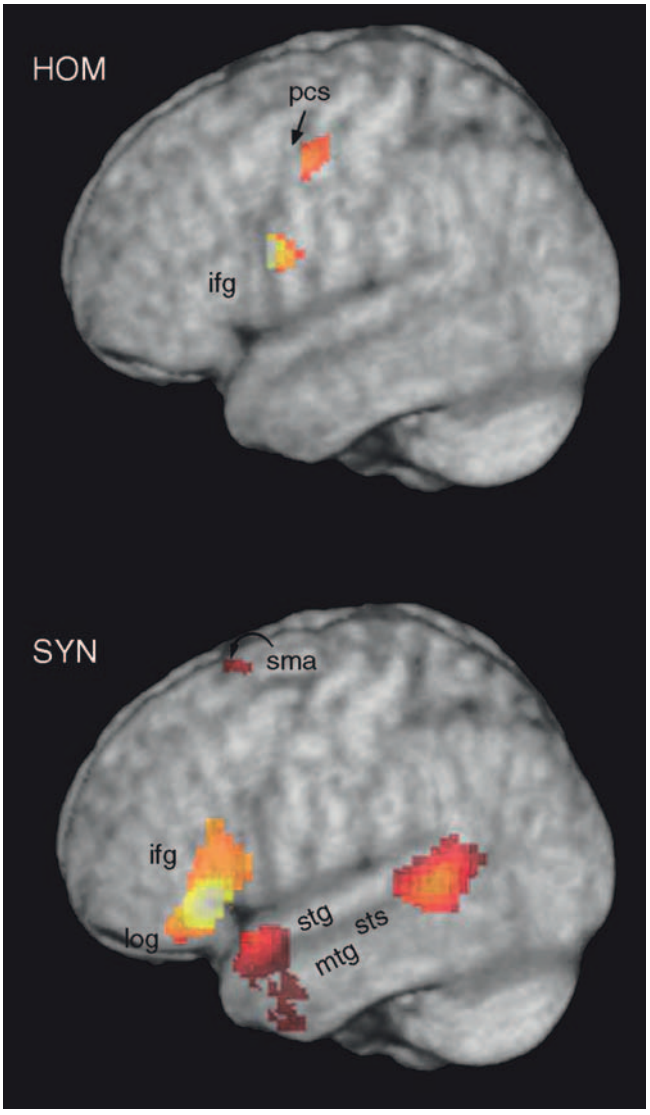


FIGURE 11.23 Word meaning activation in the left hemispheres. Above, fMRI activity for matching homonyms, words with different spelling but the same pronunciations, like 'rain' and 'reign'. Below, matching synonyms, like 'boat' and 'ship'. A control activation pattern elicited by meaningless consonant strings was subtracted from each of the fMRI activation patterns to eliminate brain activities related to reading and other common task features. Meaning-related activation (SYN, below) is far more widespread than homonym matching. Activity is prominent in the superior temporal gyrus and sulcus (STG and STS), and in the tip of the medial temporal gyrus (MTG). The inferior frontal gyrus (IFG) receives activation, as well as the lateral orbitofrontal gyrus (LOG). Higher in the left hemisphere for the SYN condition, there is some activation in the supplementary motor area (SMA), a region that is associated with the intention to act. The homonym task (HOM) also shows some activity in the posterior central sulcus (PCS). *Source*: Gitelman *et al.*, 2005.

(see Chapter 10). But it seems equally likely that word meanings are simply highly distributed, that they are inherently networks, and must therefore mobilize widely distributed regions of cortex.

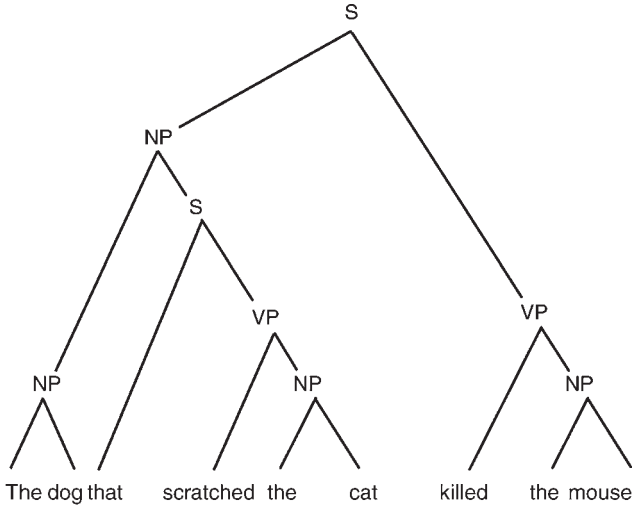


FIGURE 11.24 Syntactic tree structures allow nested propositions. A basic syntactic tree, containing an embedded clause. *Source*: Gitelman *et al.*, 2005.

This is not to say that semantics lacks a specific brain basis. A number of recording methods show high sensitivity to distinctions between words that differ in meaning. So far, however, these methods show very widespread changes in cortex (and elsewhere).

7.0 SYNTAX, NESTING, AND SEQUENCING

Syntax is often said to be the most distinctive aspect of language. Figure 11.24 shows a syntactic tree structure with a subordinate clause. Tree structures can be considered to be recursive, i.e. they can embed sentences within sentences. Although for theoretical reasons it is often supposed that syntactic recursion can go to multiple levels, the human brain is limited to one or two self-embedded clauses. That is presumably because of the capacity limits of working memory. When we develop more elaborate plans, as in the Tower of Hanoi, in chess playing, or in other complex activities, we typically use other memory aids. Thus, the sentence structure in Figure 11.24 is about typical for a single sentence. See Figure 11.25 for brain regions hypothesized to support syntactic processing.

The tree structures of sentence syntax resemble the problem-solving spaces discussed in Chapter 10 (See Box 11.3). That is not likely to be an accident. In many ways, syntax gives us a framework for planning the

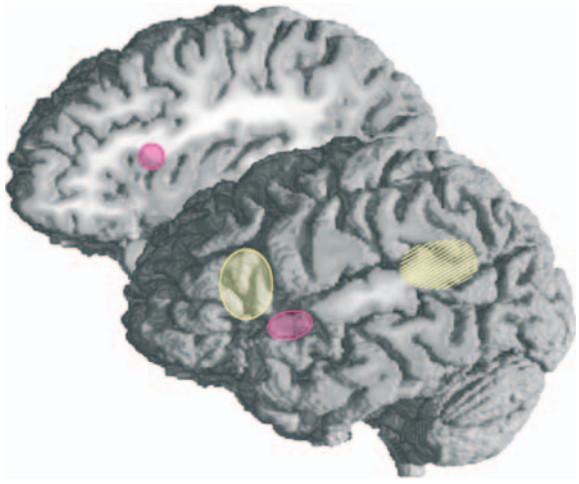


FIGURE 11.25 Syntax evokes distinctive brain regions. Grodzinsky and Friederici (2006) suggest that different cortical regions support different syntactic functions, as indicated in the figure. *Source*: Grodzinsky and Friederici, 2006.

elements of a sentence in much the way we use goals and subgoals to plan a series of actions, like navigating from one place to another, or making moves in a chess game. Syntax can therefore be seen as a cognitive planning tool, but it appears to be something human beings are adapted for. For skilled speakers, the planning of speech is of course mostly implicit (see Chapter 10).

8.0 PROSODY AND MELODY

Speaking and singing are similar activities; physically, singing is just a lengthening and tuning of vowel sounds. If you stretch out the vowels of any word – like 'cognitive neuroscience' – you are already singing in a monotone. Vary the pitch of each syllable, and you have a little song. Like language, music and dance are species-specific capacities for humans. (The biological basis for that is puzzling: language has an obvious survival function, but why music?)

Some sort of musical scale is widely used among many different cultures. All divide up the octave. In Western music, major scales are commonly perceived to be happier than minor scales. Musical notes, like the vowels of language, are based on the physics of resonant tubes, like bamboo flutes, or the tension of a bow string. When the vibrating column of air in a flute is half as long, it sounds an octave higher. When a guitar string is twice as tight, it is also heard as the same note an octave up. Small animals make high-pitched sounds and big ones low ones because of the acoustics of resonant cavities. Thus, there is a physical basis for sound perception with biological implications. It makes more sense to run away if you hear the roar of a lion than the chirp of a cricket.

Human speech also conveys emotion via intonation and sound quality. Depressed people tend to show a declining intonation contour, perhaps reflecting a lower level of subglottal air pressure. Joy is often signalled with upward inflections of sound. Emotional expression has musical intervals. Dividing up the octave is universal, though different musical cultures do it differently. Emotional expression and signaling may precede and later co-evolve with denotative language. Different musical intervals – i.e. two-tone sequences – seem to have different emotional meanings.

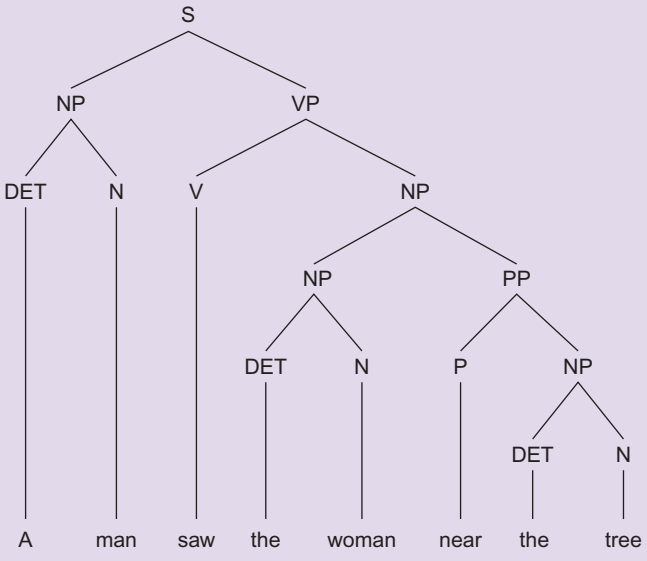
Even rhythm is an aspect of normal speech, as we can see in the stress pattern of spoken sentences: 'The *rain*/ in *Spain*/ falls *mainly*/ in the *plain*/'. You can intuitively mark the stressed syllables in any sentence. Even languages that minimize syllable stress, like French, still give a melodic shape to phrases. Babies babble in singsong, and adults spontaneously speak to young children (and pets) using exaggerated intonation. While different cultures have different musical forms, it seems likely that there are some universal (probably biological) connections between language and music.

9.0 MEANINGFUL STATEMENTS

We do not speak in single words, but in propositions – i.e. in semantically meaningful statements about the world. Syntax is tailored to enable such propositions, but even when syntax is impaired, as in some types of aphasias, people may still be able to think and express themselves propositionally. For example, aphasics may be able to point to desired food, to express discomfort or pleasure, or express any number of 'paralinguistic' statements about themselves and the world. Shastri (2002) has proposed a model of meaningful propositions encoded in a simulated neural network, based on hippocampal and cortical neurons. Figure 11.26 gives an idea of how different neurons might express different parts of a proposition. By coordinating the firing of these neurons (for example, by way of gamma synchrony), one can suggest how full propositions might be expressed in the brain.

BOX 11.3 Some basics of syntax

The building blocks of syntactic knowledge

Operation	Description	Examples
Basic relationships among words and phrases		
LEX	Lexical relations that have syntactic relevance. For example, an argument structure of a verb – the types and numbers of arguments that natural language predicates require.	1. argument: *He* ran/slept/died 2. arguments: *He* saw/hit/followed *Mary* 3. arguments: *He* gave/sent/mailed *Sue presents*
MERGE	A class of highly constrained structure-building operations, which analyze sentences into hierarchical structures. This example shows how syntactic *MERGE* rules build a sentence from the set of lexical categories ('numeration'). *MERGE* creates phrasal nodes (NP = noun phrase, VP = verb phrase, PP = prepositional phrase) out of merged categories (DETerminer Noun, Verb, Preposition), which are in turn merged into a 'root', sentence node.	Numeration: (DET = *a*, *the*; N = *man*, *woman*, *tree*; V = *saw*; P = *near*) Result of Iterated MERGE: 
Dependency relations within a sentence		
$MOVE_{XP}$	A central syntactic operation on trees (created by *MERGE*). It links an audible phrase XP (=NP, VP, PP) to one or more silent, yet syntactically active, position(s) '■' in the representation of the same sentence.	Sam knows that the saw the ballet dancer on Monday ⇒ Which dancer does Sam know that he saw ■ on Monday?
$MOVE_{V}$	A movement relationship that links distinct positions a verb might occupy. Only one is audible; the rest are silent (' '). This relation is shown in English yes/no questions, and in German, in which the verb 'sah' (saw) and its participle 'gesehen' (seen) occupy different positions.	*English*: John is tall ⇒ is John ♦ tall? *German*: Hans hat Maria gesehen ⇒ Hans sah Maria ♦ ⇒ Gestem Sah Hans ♦ Maria ♦
BIND	A relationship that determines how reflexives and pronouns link to other NPs, on which they depend for reference, in the same sentence.	John looked at himself Mary asked John to help her

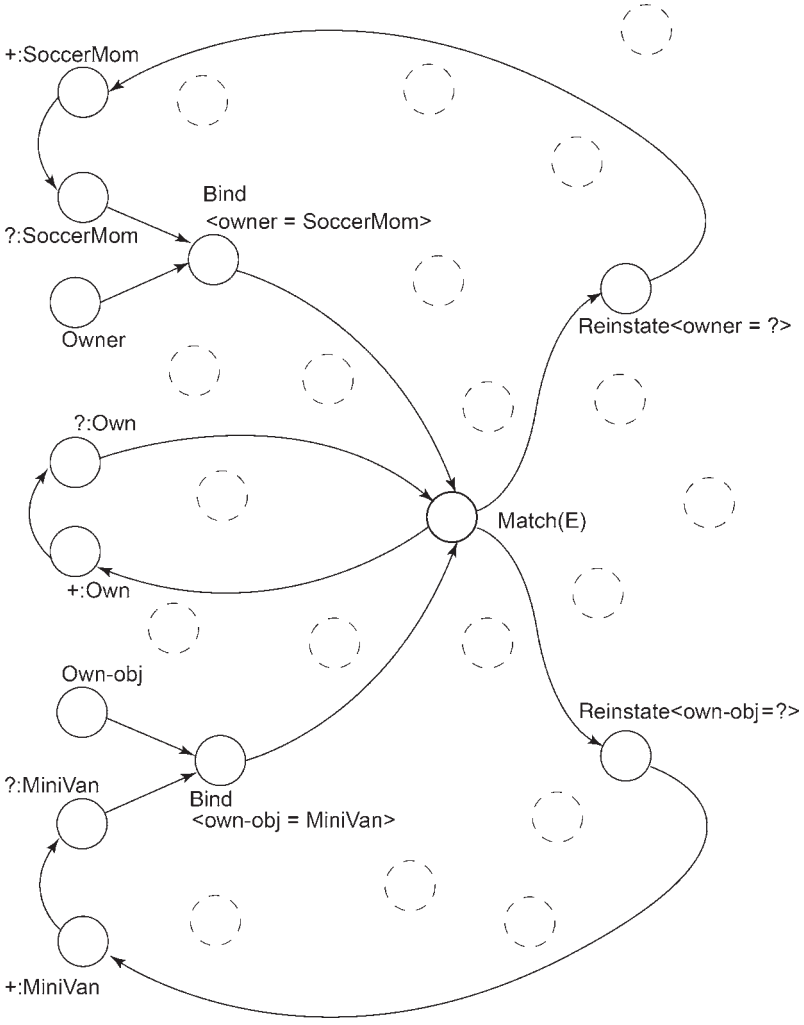


FIGURE 11.26 A proposition may involve a distributed brain network. At the level of neural networks, the proposition, 'Soccer moms are likely to own minivans' may be represented by a collection of neural populations corresponding to the main elements of the proposition: minivans, moms, soccer, relationships like 'owner-of', and the like. Such propositional networks have not been observed in the brain. The model simply suggests neural nets as we understand them. *Source*: Shastri, 2002.

10.0 UNIFIED REPRESENTATIONS OF LANGUAGE

In the 19th century, the psychologist Wilhelm Wundt suggested that language production begins with a *Gesamtvorstellung*, a unified mental representation of a sentence one was about to utter (Blumenthal, 1979). This unified representation would need many different levels of description: semantic, syntactic, phonemic, perhaps vocal, pragmatic (i.e. involving one's goals), and more. Once this many-layered tower of brain activations was ready, it would begin issuing vocal commands to move the parallel structure of the unified representation into a long series of vocal gestures. Figure 11.27 shows a contemporary example of the same basic idea. Notice that there are many simultaneous or overlapping levels of description and control, each presumably reflected in something like a set of neural arrays. In this case, each level is associated with a distinctive signal in the evoked potential (Friederici, 2002). For example, semantic information is known to evoke a large negative wave 400 ms after the onset of a stimulus (called N400).

If that seems awesomely complex, that is probably accurate. It is always useful to remember that language as we know it appears to be a distinctively human achievement. The human lineage separated from other hominids some 3 million years ago, and it is often suggested that the basic elements of human intelligence, such as language, persistence in problem-solving, cooperative and competitive behavior, and the like, may have emerged on the order of 100,000 years ago. While our vocabulary, for example, is the result of centuries of cultural development, the biological preparedness of our brains and bodies for such developments has many

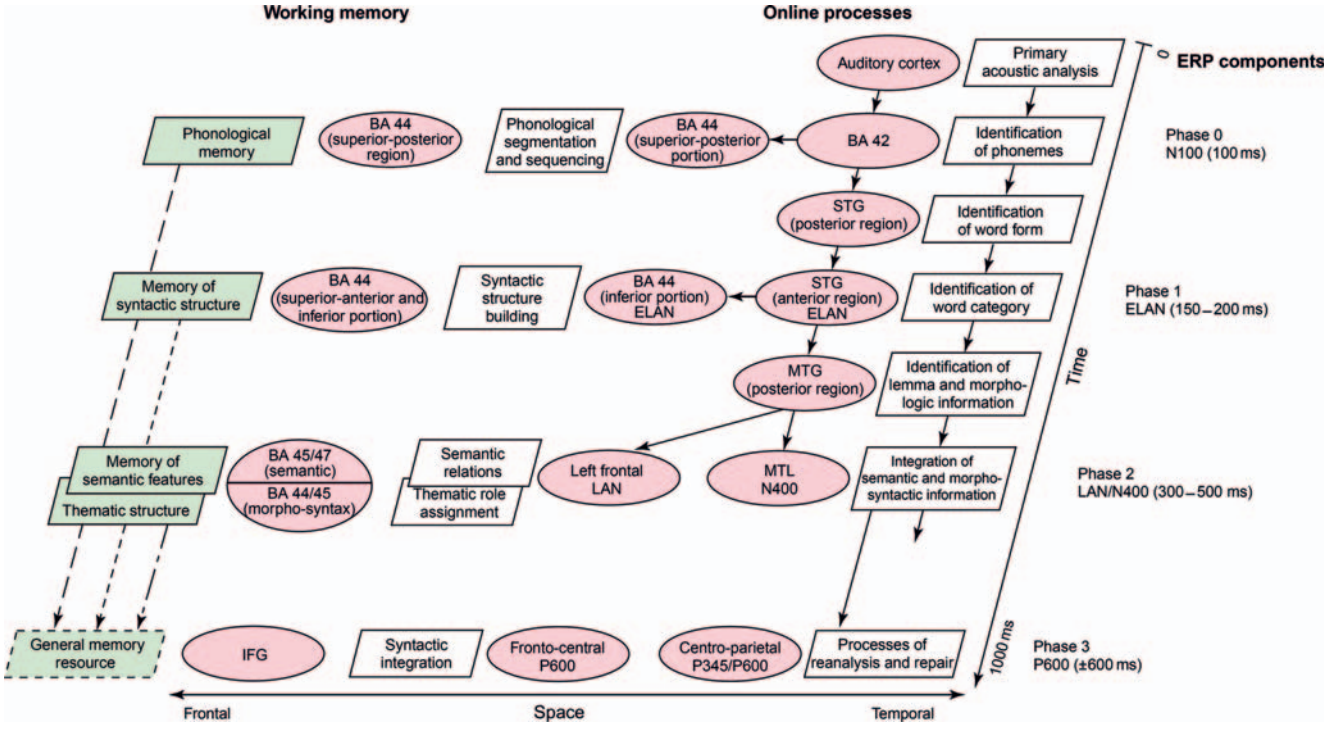


FIGURE 11.27 Putting it all together. A neurocognitive model of auditory sentence processing. The boxes represent the functional processes; the ellipses the underlying neural correlate identified either by fMRI, PET, or ERPs. The neuroanatomical specification (indicated by text in parentheses) is based on either fMRI or PET data. The ERP components specified in their temporal structure (left-hand side) are assigned to their neural correlation by the function rather than the localization of their generator. Abbreviations: BA, Brodmann's area; ELAN, early left-anterior negativity; ERP, event-related brain potential; fMRI, functional magnetic resonance imaging; IFG, inferior frontal gyrus; MTG, middle temporal gyrus; MTL, middle temporal lobe; PET, positron imaging tomography; STG, superior temporal gyrus. *Source*: Friederici, 2002.

evolutionary layers, some shared with other mammals, others with land-dwelling vertebrates. The kind of complexity we see displayed in Figure 11.27 evolved over many generations.

Chapters 3 and 6 showed that the visual system appears to have at least one region of integration 'where everything comes together', the inferotemporal cortex (area IT) (Sheinberg and Logothetis, 1997). In that area, neurons respond not to single retinal stimuli, nor to separate features like colors or light edges, but rather to entire visual objects. It is at least possible that language may have a similar region of integration (Hagoort, 2005; Figure 11.28).

The notion of a place 'where everything comes together' for some brain function is attractive and can be modeled in neural networks (e.g. McClelland, 1986; Shanahan, 2005) as well as in symbolic models of cognition (Baars and Franklin, 2003). It is an ancient idea, going back at least to Aristotle, who proposed that human cognition must have a way to combine information from the special senses like vision and hearing into single multimodel objects in the world – the guitar that you can see, touch, and listen to (Baars, 1988). Aristotle suggested that there must be a 'common sense' – some central sensory modality that combines all the special senses into a single medium. That is indeed one plausible account of multimodal regions of the parietal and frontal lobes. However, many brain regions show hub-like neuronal connections, ranging from the brainstem reticular formation to the amygdala, entorhinal cortex, prefrontal lobes, and thalamus. Some theorists suggest that the entire cortex, or the thalamo-cortical system, should be viewed as massive networks for integrating, differentiating, and distributing signals (e.g. Edelman, 1989; Edelman and Tononi, 2000; Freeman, 2004). One can imagine a brain consisting of hubs of hubs, consistent with some of the concepts of consciousness discussed in Chapter 8. Hagoort's notion of the left IFG as one anatomical hub for integrating language and meaning appears to be one version of this general idea. However, as pointed out above, attractive and plausible ideas do not constitute proof, and this hypothesis requires additional evidence.

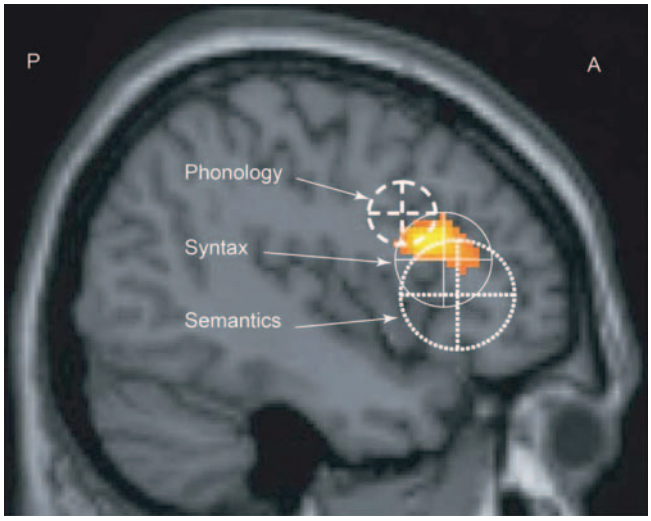


FIGURE 11.28 An area of integration? Hagoort (2005) points out that Broca's area has multiple functions which go beyond the control of speech. Nevertheless, he suggests that an expanded version of Broca's area may be considered an area for unification of speech and semantic information. To avoid confusion with the traditional concept of Broca's area, this part of cortex is referred to by its location as the left inferior frontal gyrus (L-IFG). *Source*: Hagoort, 2005, Figure 5.

11.0 SUMMARY

Language is a distinctive human capacity, one that makes it possible to transmit culture across time and space. The brain bases of language are still being clarified, but the discoveries of 19th century neurology continue to be important starting points. Broca's area for speaking and Wernicke's for speech comprehension are only part of large cortical regions involved. Current work has expanded and fractionated the traditional language areas, so that the left inferior frontal gyrus (L-IFG) is a more appropriate term for Broca's area, and posterior auditory and speech regions of the parietal and temporal cortex are more accurate than the term 'Wernicke's area'. However, there is constant interplay between frontal and posterior language areas, and a hard-and-fast division is to some extent artificial. In addition, the evidence is strong that the right hemisphere has its own role to play in language perception.

Each level of linguistic description has neuroimaging evidence in its favor (see Figure 11.1). Nonetheless, we do not have the kind of detailed knowledge of language cortex that we have for vision. One major reason is the absence of an appropriate animal model, like the macaque monkey for vision. However, recent techniques that are appropriate for humans are beginning to approach the right level of detail, and we may soon find such things as speech feature sensitive arrays of neurons, for both speech input and output.

So much of speech and language is dependent on long-term memory, however, that many scientists believe that we must ultimately look for highly distributed cortical networks to account for the vocabulary, syntax, and semantics of language. These networks are believed to depend upon the synaptic connectivities of very large numbers of neurons. Current techniques are just beginning to be able to assess such web-like patterns of distributed neurons.

12.0 PRACTICE DRAWINGS AND STUDY QUESTIONS

1. Fill in the labels in Figure 11.29 of processing hierarchies of language.
2. Give examples of the need for 'top-down' or 'expectation-driven' processing in the input flow of speech. What about the output flow?
3. What evidence is there for biological preparedness of human language capacity?
4. In what respects does the human vocal apparatus resemble a musical instrument?
5. In Figure 11.30, show the following:
   a. A cortical region likely to be involved in speech perception
   b. One for speech planning
   c. One for motor control of the vocal tract, such as the tongue
   d. One for coordinating perception and production (you may have to draw it in).
6. What role, if any, does the right hemisphere play in language?
7. What is the approximate size of the lexicon (vocabulary of natural language)? What do we know about the organization of this number of words and meaning?
8. Explain a syntactic ambiguity. What do ambiguities imply about the nature of language processing?

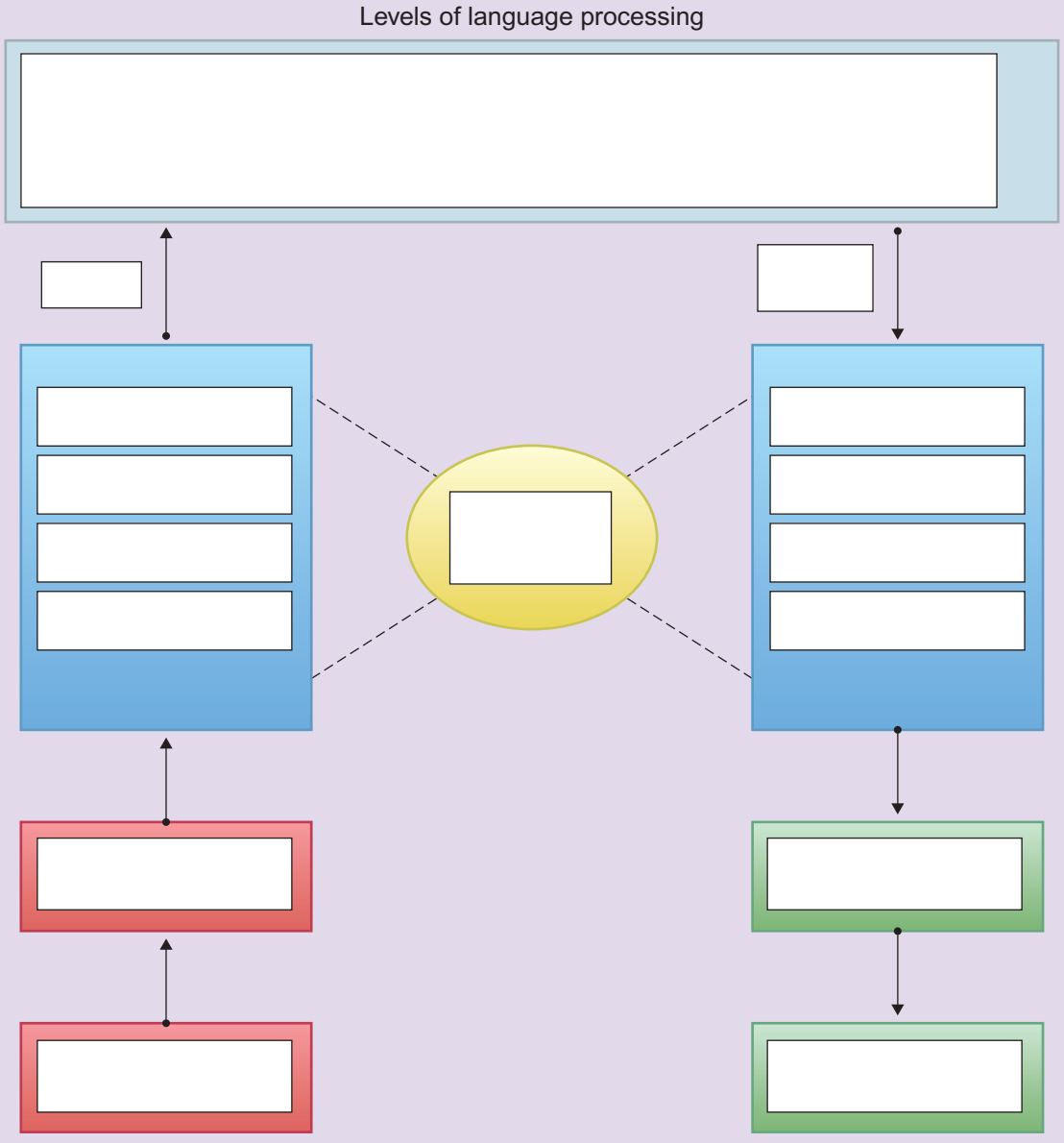


FIGURE 11.29 Linguistic processing hierarchy.

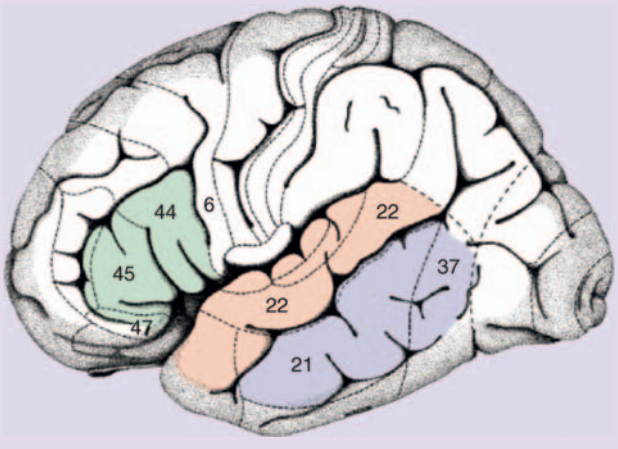


FIGURE 11.30

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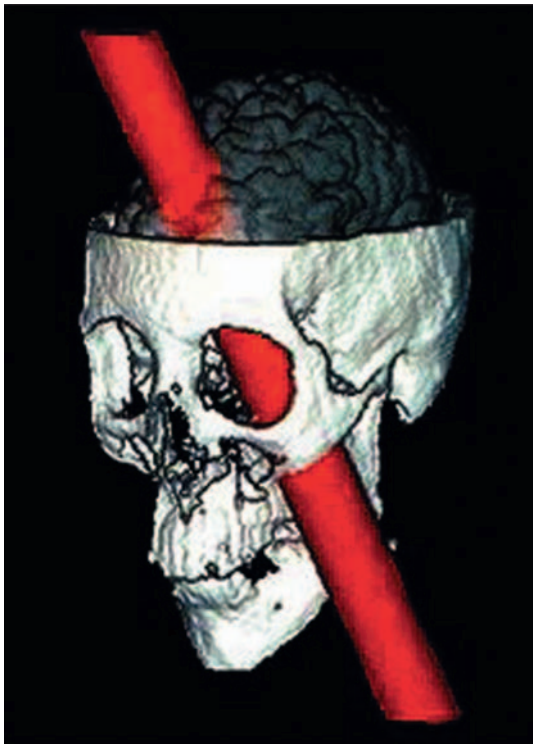
He is fitful, irreverent, indulging at times in the grossest profanity (which was not previously his custom), manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires. . . . A child in his intellectual capacity and manifestations, he has the animal passions of a strong man. . . . His mind was radically changed, so decidedly that his friends and acquaintances said he was 'no longer Gage'.

Harlow JM. Recovery from the passage of an iron bar through the head. *Publ Mass Med Soc* 1868; 2: 327–347. Quoted in: *BMJ* 1998; 317: 1673–1674 (19 December) *'No longer Gage': an iron bar through the head.*



A reconstruction of the injury to Phineas Gage. A reconstruction of Phineas Gage's railroad accident in 1848, when he was 25 years old. Notice likely damage to orbitofrontal and medial frontal regions as well. Injuries like this create damage from swellings, bleeding, heat, infection, inflammation, and physical twisting of tissues that extend far beyond the immediate region of impact. Thus, we do not really know the extent of brain damage in this classic neurological patient. *Source*: Squire *et al.*, 2003.

CHAPTER

12

Goals, executive control, and action

OUTLINE

1.0 INTRODUCTION

What do these behaviors have in common? Remembering your friend's new cell phone number while looking for a piece of paper. Deciding to study first and play basketball second. Planning a new route when a road has been closed for repair. Paying attention while you are reading this sentence. Changing your mind about raising the stakes in a poker game. All of these behaviors – and many more – are guided by the frontal lobes.

1.1 The many and complex frontal lobe functions

The frontal lobes have been described as a control center for functions such as paying attention selectively to one item rather than another, making plans and revising them when needed, monitoring the world around us – complex functions that are part of our everyday life. The frontal lobes also are described as the 'action lobes' where physical actions are planned and motor system activity is initiated. The frontal lobes also are described as the 'home'

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

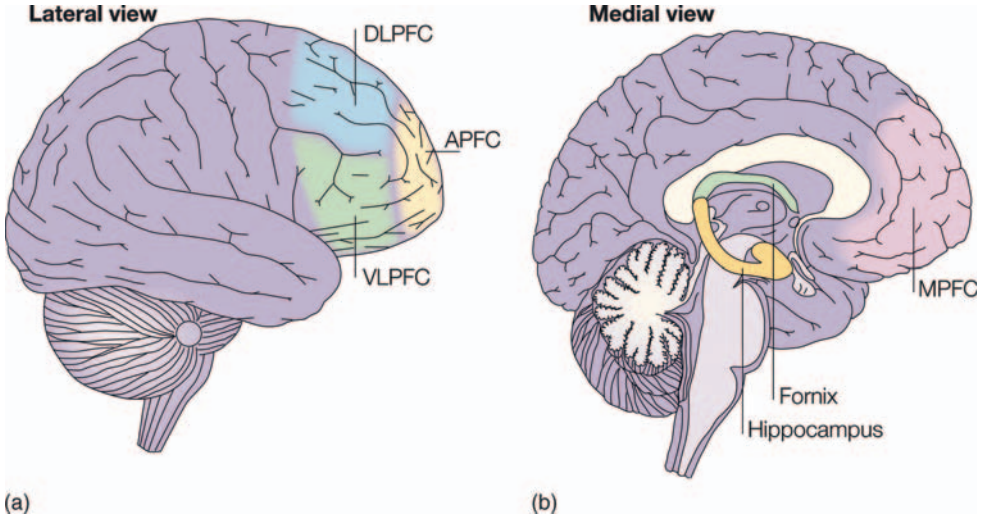


FIGURE 12.1 The major divisions of the prefrontal cortex. Prefrontal cortex can be divided into lateral (side), medial (midline), ventral (bottom), and frontal regions. The lateral division divides into upper (dorsal) and lower (ventral) halves, separated by a major horizontal fold, the inferior lateral sulcus. *Source*: Simons and Spiers, 2003.

of our personality and social morality. How does one brain region provide these diverse and complex functions?

The answer to this question is still being investigated, but we have learned about frontal lobe function through many investigative pathways. In animal research, we have learned about the role of the frontal lobe using single unit recordings. In humans, we have learned about the many roles of the frontal lobe through brain damage and disease. A key figure in our knowledge about frontal lobe function is Phineas Gage, the railroad worker who had major frontal lobe damage due to a railroad accident. Phineas' sudden personality change following the accident shed light on the role of frontal regions in personality formation and in social cognition. Studies of people who have had frontal lobe damage through disease, brain injury, or disorder have aided us in developing categories of frontal lobe function based on where the brain damage or disease has occurred and the resultant change in behavior. More recently, neuroimaging studies of healthy individuals have provided new information about the localization of patterns of frontal lobe activity occurring during tasks that tap frontal lobe functions, such as voluntary or executive attention and decision-making.

The frontal lobes are a vast mosaic of cell types and cortical regions, diverse in their cell structures, anatomical features, and connectivity patterns. Unlike regions in sensory cortex, the frontal lobes do not have a single job to do – they are not specialized for decoding speech sounds or recognizing faces. Rather, the frontal lobes are engaged in almost all aspects of human cognitive function.

In this chapter, we will present results of neuroimaging studies that have provided new data on where, what, and how specific regions in the frontal lobes are activated during cognitive tasks. Next, we will look at frontal lobe syndromes that are observed in patients with damage to the frontal lobe and connected regions. Finally, we will see how the results of neuroimaging and patient studies combine to inform us about the role of the frontal lobes in human behavior.

1.2 From the silent lobes to the organ of civilization

It took scientists many years to begin to appreciate the importance of the frontal lobes for cognition. But when this finally happened, a picture of particular complexity and elegance emerged. For the most part, this chapter will focus on the prefrontal cortex (PFC), the most anterior part of the frontal lobes, in front of the motor areas. There are many subregions in the PFC, but four regions most typically are identified when assessing their functional role in cognition: *dorsolateral PFC* (DLPFC), *ventrolateral PFC* (VLPFC), *anterior PFC* (APFC), and *medial PFC* (MPFC) (Figure 12.1).

PFC is located in front of the primary motor cortex, sometimes called the motor strip. The frontal lobes used to be known as 'the silent lobes' because they are not easily linked to any single, easily defined function. Over the last decades, however, new imaging techniques are suggesting more specialized regions within the PFC for functions like executive control, conflict monitoring, emotion, and working memory. There is still considerable debate about these issues, however.

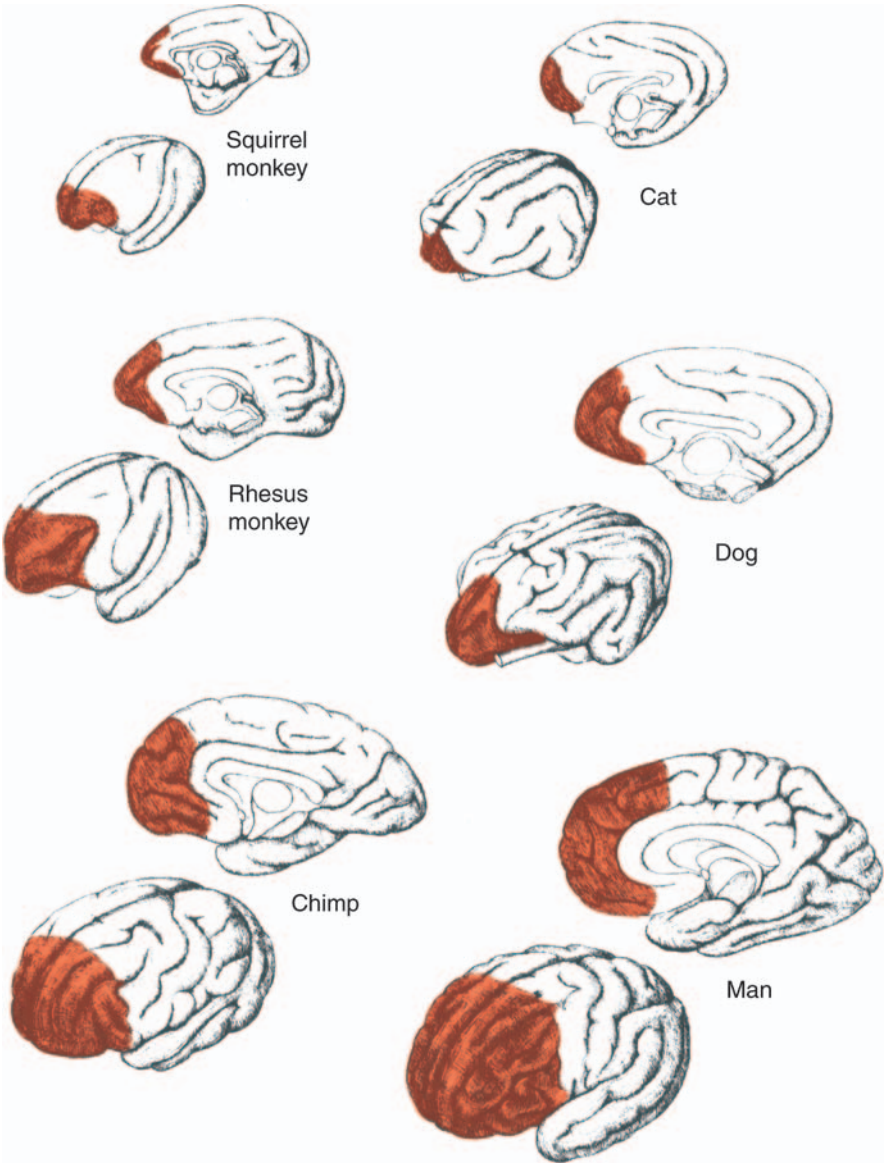


FIGURE 12.2 The prefrontal cortex expands over mammalian and primate evolution. A greatly enlarged prefrontal cortex is a distinctively human and primate feature. Other large-brained mammals like whales and dolphins have expanded parietal rather than prefrontal regions. Bottom right, a human brain, with a chimp brain on the bottom left. *Source*: Squire *et al.*, 2003.

2.0 PHYLOGENY AND ONTOGENY

If it seems to you that the role the frontal lobes play in cognition seems uniquely human, you are right! The vast expansion of the frontal lobes during evolution and their maturational path during the lifetime in humans are unique among living creatures.

2.1 Phylogeny

In evolution, the frontal lobes accelerated in size only with the great apes. These regions of cortex underwent an explosive expansion at the late stage of evolution. According to Brodmann (1909), the PFC or its analogs account for 29% of the total cortex in humans, 17% in the chimpanzee, 11.5% in the gibbon and the macaque, 8.5% in the lemur, 7% in the dog, and 3.5% in the cat (Figure 12.2). While whales and dolphins have large brains, it is the *parietal* rather than frontal cortex that has expanded in these aquatic mammals.

2.2 Ontogeny

As the seat of goals, foresight, and planning, the frontal lobes are perhaps the most uniquely human of all the components of the human brain. In 1928, the neurologist Tilney suggested that all human evolution should be considered the 'age of the frontal lobe', but scientific interest in the PFC was late in coming.

TABLE 12.1 Some common prefrontal functions

1	Planning, setting goals, and initiating action
2	Monitoring outcomes and adapting to errors
3	Mental effort in pursuing difficult goals
4	Interacting with other regions in pursuit of goals (basal ganglia, thalamic nuclei, cerebellum, motor cortex)
5	Having motivation, being willing to engage in action
6	Initiating speech and visual imagery
7	Recognizing others people's goals, engaging in social cooperation and competition
8	Regulating emotional impulses
9	Feeling emotions
10	Storing and updating working memory
11	Active thinking
12	Enabling conscious experiences (Deheane, 2001)
13	Sustained attention in the face of distraction
14	Decision-making, switching attention and changing strategies
15	Planning and sequencing actions
16	Unifying the sound, syntax, and meaning of language
17	Resolving competition between plans

Only gradually did it begin to reveal its secrets to the great scientists and clinicians like Hughlings Jackson (1884) and Alexander Luria (1966), and in the last few decades to researchers like Antonio Damasio (1993), Joaquin Fuster (1997), Patricia Goldman-Rakic (1987), Donald Stuss and Frank Benson (1986), and others.

3.0 FUNCTION OVERVIEW

If the frontal lobes are the 'organ of civilization', then what exactly is their function? What is their 'civilizing' effect? The functions of the frontal lobes defy a simple definition. They are not invested with any single, ready-to-label function. A patient with frontal-lobe damage will typically retain the ability to move around, use language, recognize objects, and even memorize information. However, PFC plays the central role in forming goals and objectives and then in devising plans of action required to attain these goals. It selects the cognitive skills needed to implement the plans, coordinates these skills, and applies them in a correct order. Finally, the PFC is responsible for evaluating our actions as success or failure relative to our intentions (Table 12.1).

3.1 'Memory of the future'

David Ingvar (1985) coined the phrase: 'Memory of the future'. Ingvar was referring to one of the most important functions of advanced organisms: making plans and then following the plans to guide behavior. Unlike primitive organisms, humans are active, rather than reactive, beings. The transition from mostly reactive to mostly proactive behavior is among the central themes of the evolution of the nervous system. We are able to form goals, our visions of the future. Then we act according to our goals. But, in order to guide our behavior in a sustained fashion, these mental images of the future must become the content of our memory; thus the 'memories of the future' are formed.

Human cognition is forward-looking, *proactive* rather than *reactive*. It is driven by goals, plans, hopes, ambitions, and dreams, all of which pertain to the future and not to the past. These cognitive powers depend on the frontal lobes and evolve with them. The frontal lobes endow the organism with the ability to create neural models as a prerequisite for making things happen, models of something that, as of yet, does not exist but which you *want* to bring into existence.

To makes plans for the future, the brain must have an ability to take certain elements of prior experiences and reconfigure them in a way that does not copy any actual past experience or present reality exactly. To accomplish that, the organism must go beyond the mere ability to *form* internal representations, the models of the world outside. It must acquire the ability to *manipulate and transform* these models. We can argue that tool-making, one of the fundamental distinguishing features of primate cognition, depends on this ability, since a tool does not exist in a ready-made form in the natural environment and has to be *imagined* in order to be made. The neural machinery for creating and holding 'images of the future' was a *necessary prerequisite* for tool-making, and thus for launching human civilization.

We can also argue that the generative power of language to create new ideas depends on this ability as well. The ability to manipulate and recombine internal representations depends critically on the PFC, which probably made it critical for the development of language.

3.2 Self-awareness and executive function

Goal formation is about 'I need' and not about 'it is'. Therefore, the ability to formulate goals must have been inexorably linked to the emergence of the mental representation of self. It should come as no surprise that *self-awareness* is also intricately linked to the frontal lobes.

All these functions can be thought of as metacognitive rather than cognitive, since they do not refer to any particular mental skill, but provide an overarching organization for all of them. For this reason, some authors refer to the functions of the frontal lobes as *executive functions*, by analogy with a governmental or corporate executive.

4.0 CLOSER LOOK AT FRONTAL LOBES

As we have mentioned, the neuroanatomy and neurophysiology of the frontal lobes reflect their diverse and complex functions, with many distinct regions that differ sharply in their cellular and anatomical structure. Adding another layer of complexity is their high degree of connectivity across many brain regions. In this section, we highlight the main subdivisions of the frontal lobes and show the amazing neural highways that connect them to the rest of the brain.

4.1 Neuroanatomy and neurophysiology of the frontal lobes

The boundaries of the frontal lobes typically are described using gross anatomical structures and Brodmann areas to define boundaries of frontal lobe regions. On the surface of cerebral cortex the following boundaries are used to delimit the frontal lobes: on the dorsolateral surface of the brain they lie just in front of the demarcation line formed by the *lateral* (or *Sylvian*) *fissure and the central sulcus*; medially, the boundaries are roughly formed by the continuation of the central sulcus to the mediodorsal surface of the brain, and by an imaginary line corresponding to a projection of the lateral fissure to the medioventral surface of the brain (Carpenter and Parent, 1995).

4.2 How prefrontal cortex is defined

A more precise definition of PFC can be accomplished by using *Brodmann area* maps (Brodmann, 1909). Brodmann areas are based on the types of neurons and connections that typically are found there within. According to this definition, the PFC consists of Brodmann areas 8, 9, 10, 11, 12, 13, 44, 45, 46, and 47 (Fuster, 1997; Figure 12.3). These areas are characterized by the predominance of the so-called granular neural cells found mostly in layer IV (Campbell, 1905, in Fuster, 1997).

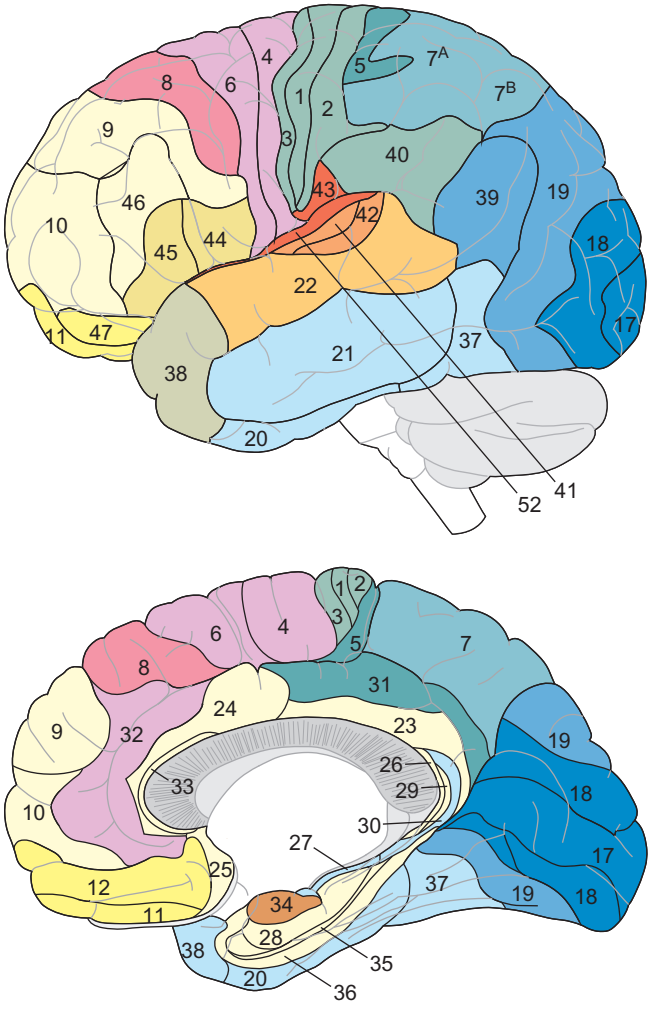


FIGURE 12.3 Brodmann areas in the frontal lobes. Areas forward of motor cortex are considered to be prefrontal. (Brodmann areas 4 and 6 are motor and premotor regions.) However, the boundary is not rigid. It is often useful to think of a gradual transition between more 'cognitive' areas and primary motor cortex (BA 4), which directly controls voluntary muscles. *Source*: Adapted by Bernard J. Baars from M. Dubin, with permission; drawn by Shawn Fu.

Another method of outlining the PFC is through its subcortical projections. The dorsomedial thalamic nucleus is, in a sense, the point of convergence, the 'summit' of the integration occurring within the specific thalamic nuclei (Figure 12.4). PFC is then defined as the area receiving projections from the dorsomedial thalamic nucleus.

Finally, the PFC sometimes is delineated through its biochemical pathways. According to that definition, the PFC is defined as the area receiving projections from the mesocortical dopamine system. The various methods of delineating the PFC outline roughly similar territories.

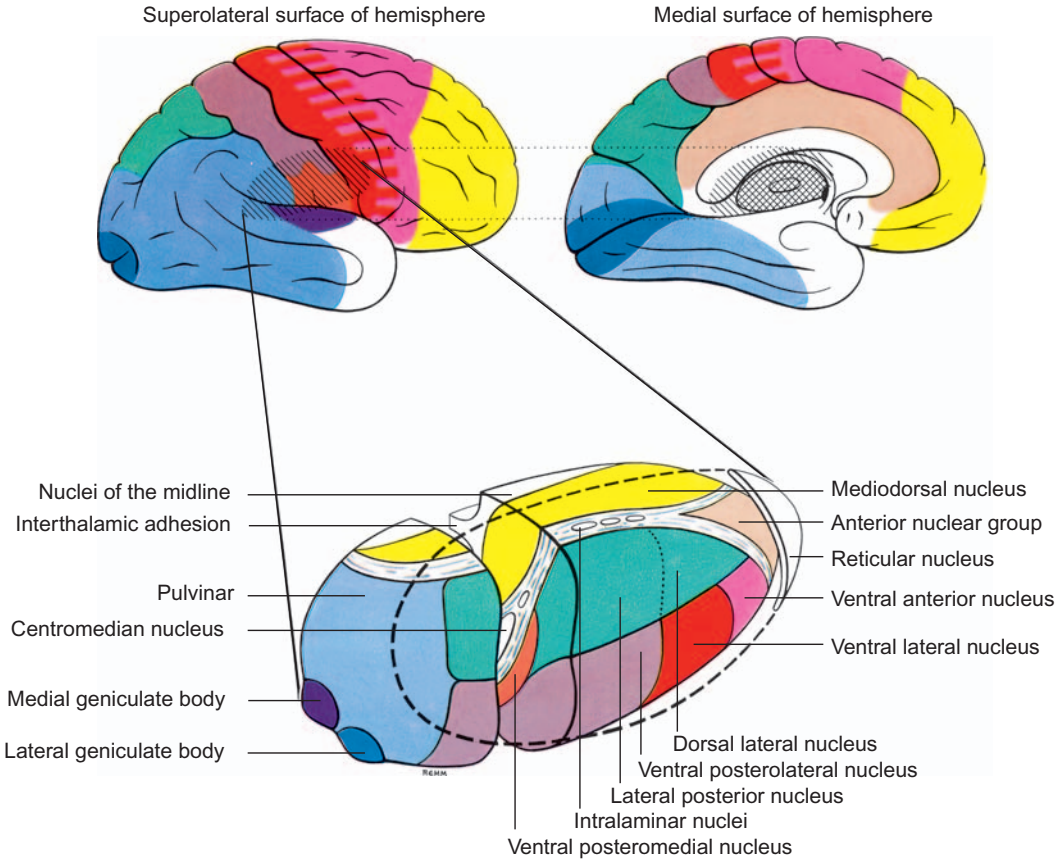


FIGURE 12.4 Prefrontal cortex is also defined by major thalamic connections. The yellow cortical areas are considered to be prefrontal because of their connections with mediodorsal nucleus of the thalamus. Many scientists believe that the connections between cortex and thalamus are so close and intimate that thalamic nuclei can be considered to be additional layers of cortex. Thus, we are looking at a thalamo-cortical system. *Source*: Standring, 2005.

4.3 The vast connective highways of the frontal lobes

The PFC is connected directly with every distinct functional unit of the brain (Nauta, 1972). It is connected to the highest levels of perceptual integration, and also with the *premotor cortex*, *basal ganglia*, and the *cerebellum*, all involved in aspects of motor control and movements. PFC also is connected with the *dorsomedial thalamic nucleus*, often considered to be the highest level of integration within the thalamus; with the *hippocampi* and *medial temporal structures*, known to be critical for memory; and with the *cingulate cortex*, believed to be critical for emotion and dealing with uncertainty. In addition, PFC connects with the *amygdala*, which regulates most emotions and social cognition, and with the *hypothalamus*, in charge of control over the vital homeostatic functions of the body. Finally, PFC is also well connected with the *brainstem* nuclei involved in wakefulness, arousal, and overall alertness, regulation of sleep and REM dreams. A schematic (and by no means exhaustive) representation of this complex connectivity is depicted in Figure 12.5.

This unique connectivity makes the frontal lobes singularly suited for coordinating and integrating the work of other brain structures (Figure 12.6). This extreme connectivity also puts the frontal lobes at a particular risk for disease. Some scientists believe that the PFC contains a map of the whole cortex, an assertion first made by Hughlings Jackson (1884) at the end of the nineteenth century. This hypothesis asserts that prefrontal regions are needed for normal consciousness. Since any aspect of our mental world may, in principle, be the focus of our consciousness, it stands to reason that an area of convergence of all its neural substrates must exist. This leads to the provocative proposition that the evolution of consciousness, the highest expression of the developed brain, parallels the evolution of the PFC.

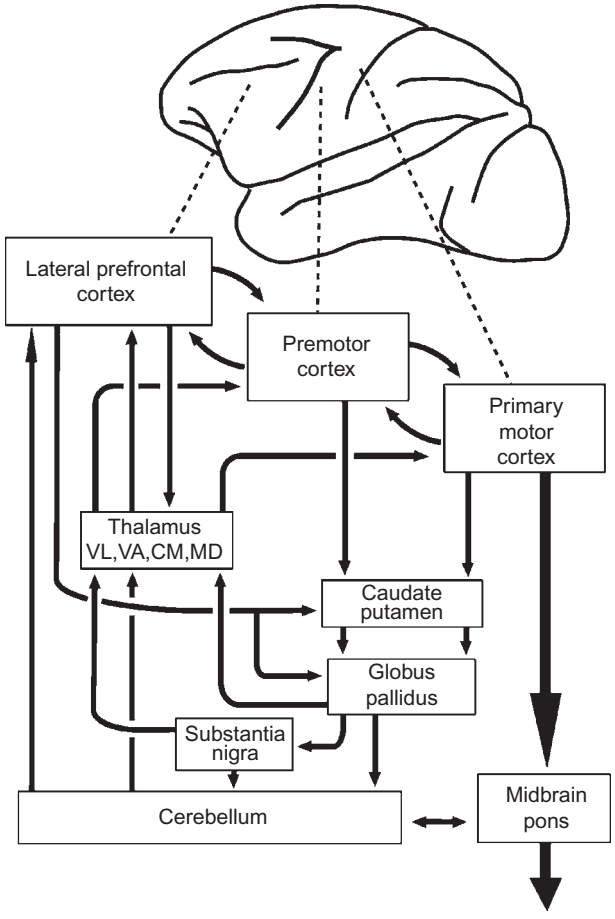


FIGURE 12.5 Connectivity of the prefrontal cortex with structures involved in motor function. The three lateral frontal regions of the motor hierarchy (prefrontal, premotor, motor cortices) are interconnected with thalamus, basal ganglia, and cerebellum by recurrent axonal loops that are essential to motor control. Abbreviations: CM, central median nucleus; MD, mediodorsalis nucleus; VA, anteroventral nucleus; VL, ventrolateral nucleus. *Source*: Fuster, 2008.

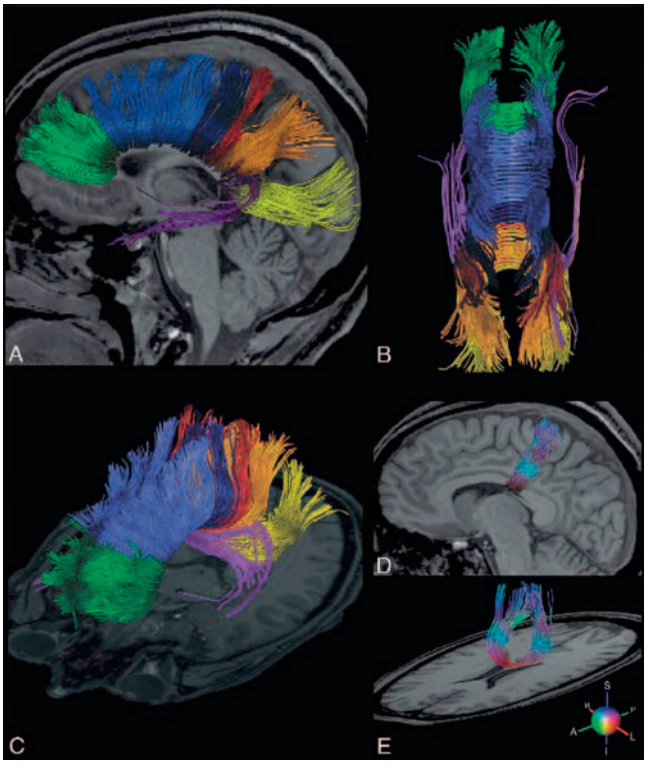


FIGURE 12.6 A. Midsagittal view of the fiber bundles extending into the prefrontal cortex, shown in green, and into the premotor and motor cortex, shown in blue. B. An axial view of the same fiber bundles. *Source*: Hofer & Frahm, 2006.

5.0 A CLOSER LOOK AT FRONTAL LOBE FUNCTION

5.1 Executive functions

As mentioned earlier, currently, the concept of executive functions is inextricably linked to the function of the frontal lobes. The groundwork for defining the executive functions system was laid by Alexander Luria as early as 1966 (Luria, 1966). At the time, Luria proposed the existence of a system in charge of intentionality, the formulation of goals, the plans of action subordinate to the goals, the identification of goal-appropriate cognitive routines, the sequential access to these routines, the temporally ordered transition from one routine to another, and the editorial evaluation of the outcome of our actions (Figure 12.7).

Subsequently, two broad types of cognitive operations linked to the executive system figured most prominently in the literature:

1. An organism's ability to guide its behavior by internal representations (Goldman-Rakic, 1987) – the formulation of plans and then guiding behavior according to these plans
2. An organism's ability not only to guide its behavior by internal representations, but also the capacity of 'switching gears' when something unexpected happens (Milner, 1982).

To deal effectively with such transitions, a particular ability is needed – *mental flexibility* – that is the capacity to respond rapidly to unanticipated environmental contingencies. Sometimes this is referred to as an ability to shift *cognitive set*. Additionally, the executive system is critical for planning and the generative processes (Goldberg, 2001).

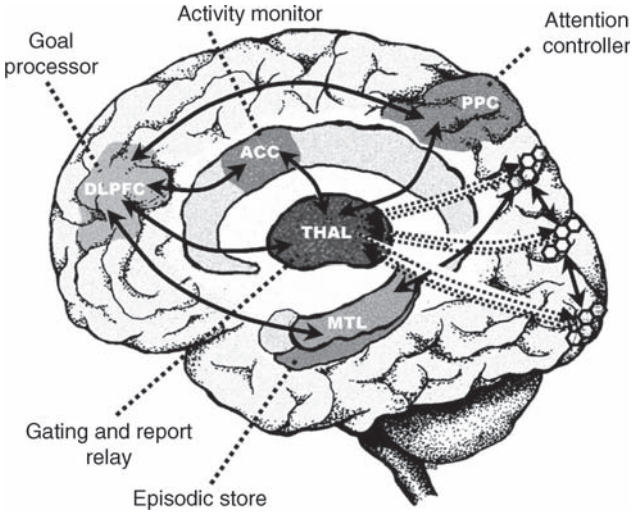


FIGURE 12.7 Prefrontal lobes coordinate goals and actions. An integrated model of goal processing in the prefronal cortex (the dorsolateral part), connecting to the anterior cingulate to resolve conflicts. Memory is involved in retrieving stored action plans and contextual information (temporal lobe and MTL), and the posterior parietal cortex is considered as a control of spatial attention, needed for actions. The thalamus serves as a hub for multiple functions. *Source*: Schneider and Chein, 2003.

Fuster (1997) enlarged on the premise originally developed by Luria by suggesting that the so-called executive systems can be considered functionally homogeneous in the sense that they are in charge of actions, both external and internal (such as logical reasoning). In general, the executive functions are not unique to humans. However, the uniqueness of the human executive functions is in the *extent* to which they are capable of integrating such factors as time, informational novelty, and complexity, and possibly ambiguity.

5.2 Social maturity and moral development

While many neuroimaging and behavioral studies have investigated attention, working memory, and executive control processes in the PFC, the frontal lobes also play a critical role in the development of social cognition – a key link to the role of the frontal lobes as the 'organ of civilization'. The capacity for volitional control over one's actions is not innate, but it emerges gradually through development and is an important, perhaps central, ingredient of *social maturity*.

5.2.1 Early life experience and orbitofrontal cortex development

Allan Schore (1999) believes that early mother–infant interaction is important for the normal development of the orbitofrontal cortex during the first months of life. By contrast, early-life stressful experiences permanently damage the orbitofrontal cortex, predisposing the individual to later-life psychiatric diseases. This implies that early social interactions help shape the brain. Scientists have known for years that early sensory stimulation promotes the development of visual cortex in the occipital lobes, and early-life sensory deprivation retards its development. It is possible that social stimulation is to the development of the frontal cortex what visual stimulation is to the development of the occipital cortex.

5.2.2 Moral development and the frontal cortex

Furthermore, following this logic, is it possible that moral development involves the frontal cortex, just as visual development involves occipital cortex and language development involves temporal cortex? The PFC is the association cortex of the frontal lobes, the 'action lobes'. The posterior association cortex encodes generic information about the outside world. It contains the taxonomy of the various things known to exist and helps recognize a particular exemplar as a member of a known category. By analogy, the PFC may contain the taxonomy of all the *sanctioned, moral actions and behaviors*. And could it be that, just as damage or maldevelopment of the posterior association cortex produces *object agnosias*, so does damage or maldevelopment of the PFC produce, in some sense, *moral agnosia*?

A report by Damasio and colleagues lends some support to this idea (Anderson *et al*., 1999). Damasio studied two young adults, a man and a woman, who suffered damage to the frontal lobes very early in life. Both engaged in antisocial behaviors: lying, petty thievery, truancy. Damasio claims that not only did these patients fail to act according to the proper, socially sanctioned moral precepts, but they even failed to recognize them as morally wrong.

The orbitofrontal cortex is not the only part of the frontal lobes linked to socially mature behavior. The *anterior cingulate cortex* occupies a mid-frontal position and is closely linked to the PFC. The anterior cingulate cortex traditionally has been linked to emotion. According to Michael Posner, it also plays a role in social development by regulating distress (Posner and Rothbart, 1998).

5.2.3 Age of maturity and frontal lobe development

The implicit definition of social maturity changes throughout the history of society, and so does the

time of 'coming of age'. In modern Western societies, the age of 18 (or thereabout) has been codified in the law as the age of social maturity. This is the age when a person can vote and is held responsible for his or her actions as an adult. The age of 18 is also the age when the maturation of the frontal lobes is relatively complete. Various estimates can be used to measure the course of maturation of various brain structures. Among the most commonly used such measures is pathway myelinization (Yakolev and Lecours, 1967). The frontal lobes cannot fully assume this role until the pathways connecting the frontal lobes with the far-flung structures of the brain are fully myelinated.

The agreement between the age of relatively complete maturation of the frontal lobes and the age of social maturity is probably more than coincidental. Without the explicit benefit of neuroscience, but through cumulative everyday common sense, society recognizes that an individual assumes adequate control over his or her impulses, drives, and desires only by a certain age. Until that age, an individual cannot be held fully responsible for his or her actions in either a legal or moral sense. This ability appears to depend critically on the maturity and functional integrity of the frontal lobes.

6.0 NEUROIMAGING THE EXECUTIVE BRAIN

The two broad types of cognitive operations linked to the executive systems in the frontal lobe have been extensively investigated using functional neuroimaging techniques such as PET and fMRI. We summarize some general findings here, separating the results into three sections: *attention and perception*, *working memory*, *executive function and motor control*. But first, a word of caution about functional neuroimaging studies of complex processes: as we have described, the PFC is intricately involved in many cognitive and executive processes such as paying attention, holding something in mind for a few moments, switching attention when needed, and making decisions. Thus, *any task* used in a neuroimaging study will necessarily involve these complex and overlapping processes in the frontal lobe and elsewhere in the brain. In fact, just participating in the study engages the subject – and their frontal lobes – in complicated ways (for a good discussion of these issues, see Fuster, 2008).

In order to disentangle the many processes engaged in any task, investigators studying frontal lobe function need to carefully design their studies so that they can identify which processes are specifically related to, for example, attention versus working memory, which are aspects of almost any task. In the following section, we present a brief summary of many neuroimaging studies that have looked at these prefrontal processes. As we stated in Chapter 4, a key approach to understanding complex brain function is to have *converging evidence* across labs and studies, where many differing tasks and subject groups provide evidence in support of a central notion or hypothesis about brain regions and networks that subserve executive processes.

6.1 Attention and perception

Imagine that you are a subject in an fMRI study. Your task is to look at a screen and when you see a picture of a male face, you are to press one button, and if you see a picture of a female face, your press another button. Easy, right? What parts of the brain will be activated by this task? You might suggest that visual cortex will be busy, based on your knowledge of sensory activity in the brain. You might also suggest that the fusiform face area (see Chapter 6) will 'light up' for this task. And you would be correct. But, there are other aspects of this task that will activate the brain: paying attention to the screen, making a decision about whether the face is male or female, preparing to press a button, and then actually pressing the button – all key aspects of frontal lobe function. In fact, this is a central finding in neuroimaging studies of visual or auditory perception – many areas in the brain outside of sensory cortex are activated.

But first, a word about attention. In this chapter about frontal lobe functions, we will be discussing *voluntary attention*: this is the aspect of attention in which we are in control of what we decide to pay attention to. When reading this sentence, for example, you are deciding to focus on the words and their meaning and not on the font type or size, or the sound of the clock ticking at your elbow. Voluntary attention often is called *executive attention* or *top-down attention* to indicate that it is the class of attentional processes that are under our control. Another type of attention is involuntary – these are automatic, frequently stimulus-induced processes whereby our attention is 'grabbed' by something in our environment. For example, the ringing of your cell, the sudden bright light when the sun comes from behind a cloud, the aroma of coffee brewing all may temporarily attract your attention without any conscious effort on your part. Automatic attentional processes

can serve to disrupt our voluntary attention, but both are critical for being able to plan and initiate behavior – whether that behavior is finishing an essay for class in the morning or jumping out of the way when a car horn sounds behind you. The push-and-pull of voluntary and involuntary attentional processes are key functions of the frontal lobes.

An early investigation used PET to show localization patterns for sustained voluntary attention and provided important new information about prefrontal regions that subserved voluntary attentional processes (Pardo, Fox, & Raichle, 1991). At about the same time, seminal work on the voluntary attentional networks involved in perceptual tasks was provided by Michael Posner and Steve Peterson (Posner & Peterson, 1990), where they detailed an anterior attentional system, which they described as having three major separable networks that perform the alerting, orienting, and executive (conflict resolution) voluntary attentional functions that are important to many tasks. Over the years, Posner and his colleagues developed an attention network test (ANT) that provided them with ways to separately measure and record brain regions that subserve these voluntary attentional networks. The anterior attentional system they describe has three key networks: *alerting* for maintaining an alert state, such as being ready to look at visual images in the scanner example above; *orienting* such as preparing to see a new visual image of a face appears in the scanner, and *executive*, such as deciding whether the face is male or female.

These networks are shown visually in the brain in Figures 12.8 through 12.10, where Figure 12.8 details fronto-parietal regions that are part of the alerting network, Figure 12.9 shows parietal lobe regions active in the orienting network, and Figure 12.10 shows frontal and many other regions active in the executive or conflict resolution network.

Another central finding from these and other studies of anterior voluntary attention networks is that the *level of activity* in the PFC corresponds to the *level of attention* required by the task, with more activity for tasks with higher attentional demands (Posner *et al*., 1988; Pardo *et al*., 1990). A part of the prefrontal region that typically is activated by tasks requiring focused attention is the anterior cingulate gyrus in the anterior cingulate cortex (ACC) (Posner *et al*., 1988; Raichle, 1994).

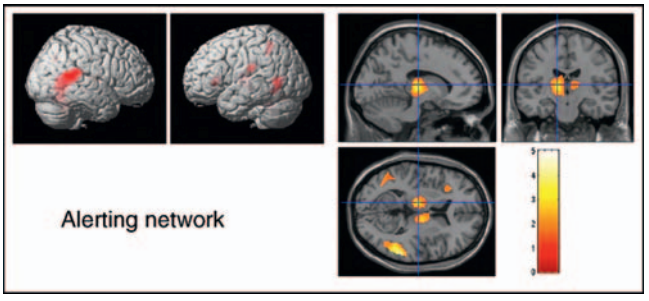


FIGURE 12.8 fMRI results for the alerting attentional network. The cross-section view of activations shows the thalamic activations of the alerting effect. *Source*: Fan *et al*., 2005.

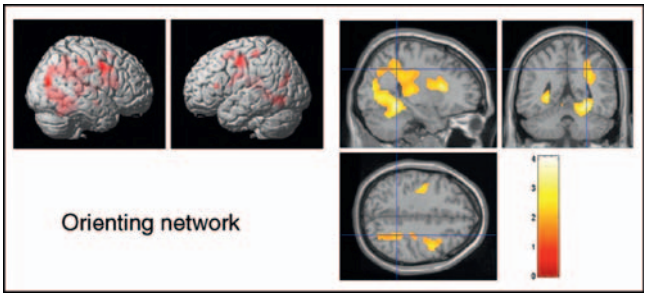


FIGURE 12.9 fMRI results for the orienting attentional network. The cross-section view of activations shows parietal activation. *Source*: Fan *et al*., 2005.

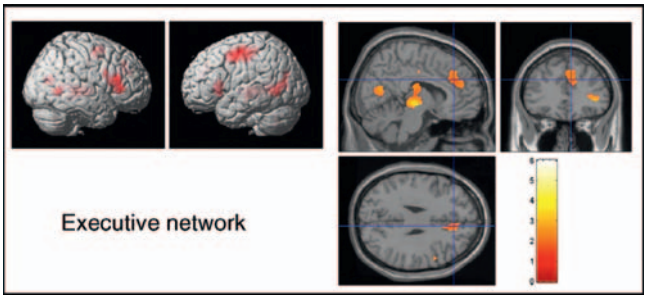


FIGURE 12.10 fMRI results for the conflict attentional network. The cross-section view of activations shows ACC activation. *Source*: Fan *et al*., 2005.

6.2 Working memory

The ability to keep something in mind for a limited amount of time is a central function in cognition. This ability – working memory – is closely associated with voluntary attentional systems. In fact, one way of describing working memory is that it serves as an *inward directed voluntary attention* system, directing attention to internal representations (Fuster, 2008). A central issue in investigating brain areas that subserve working memory is: how do you study working memory and separate findings from other executive processes such as attention and decision-making? To accomplish this, D'Esposito and colleagues developed a dual task paradigm using two tasks that,

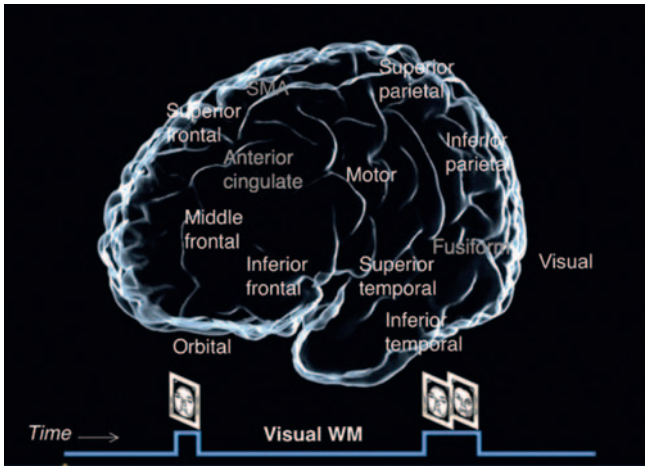


FIGURE 12.11 Outline of left cortex used in subsequent figures to mark areas activated in working memory. Areas in convexity cortex designated with white labels; those in mesial cortex with gray labels. (SMA, supplementary motor area.) Below, temporal display of a trial in a typical visual working-memory (WM) task, delayed matching-to-sample, with faces. First upward inflexion of timeline marks the time of presentation of the sample face; second inflexion that of the choice faces. Delay-memory-period, between sample and choice, lasts 20 seconds. *Source*: Fuster, 2008.

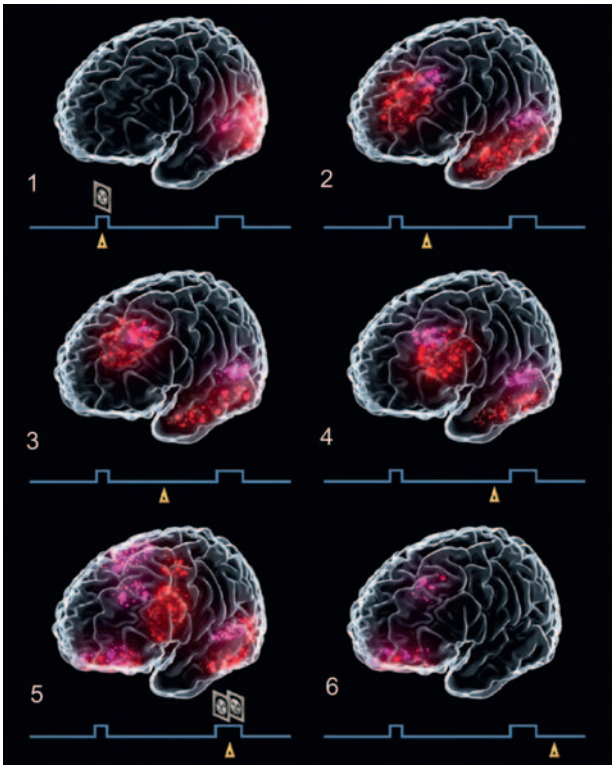


FIGURE 12.12 Relative (above-baseline) cortical activation at six moments in time (marked by yellow triangle) in the course of the visual memory task in Figure 12.11. Activations of convexity cortex in red, of medial cortex in pink. (1) At the sample, the activation is restricted to visual and posterior inferotemporal cortex; (2) in early delay, it extends to lateral prefrontal cortex, anterior cingulate, anterior inferotemporal cortex, and fusiform cortex; (3) in mid-delay, it persists in prefrontal, inferotemporal, and fusiform cortex; (4) in late delay, it migrates to premotor areas, persisting in inferotemporal and fusiform cortex; (5) at the response (choice of sample-matching face), it covers visual, inferotemporal, and fusiform cortex in the back, and extends to motor areas (including frontal eye fields), supplementary motor area (SMA), and orbitofrontal cortex in the front; (6) after the trial, activation lingers in anterior cingulate and orbitofrontal cortex. *Source*: Fuster, 2008.

individually, did not have working memory demands (D'Esposito *et al*., 1995). Together, however, they did produce working memory demands and in this way, D'Esposito and colleagues were able to isolate processes that were specific to working memory function and not to general task performance. They identified regions in the PFC that were specifically involved in working memory processes, providing important new data on separable aspects of central executive functions in PFC.

In his book, *The Prefrontal Cortex*, Fuster (2008) presents a meta-analysis of several neuroimaging studies of working memory to provide a schematic summary of brain areas involved in studies tapping visual versus verbal working memory. Results are presented in Figures 12.11 through 12.13.

Figure 12.11 shows a schematic of brain areas – both visual from the lateral view of the brain and those tucked inside – active in experiments that tap working memory processes. Figure 12.12 shows activation patterns for a visual memory task, with activity in the occipital lobe as expected for an experiment using visual stimuli, and frontal lobe regions that are active due to the nature of the task. Figure 12.13 shows a similar pattern of activation, but this time it is in response to a verbal memory task and so in this case, temporal lobe areas are active due to the auditory stimuli, along with frontal lobe regions.

One hypothesis that has been put forth about the role of working memory systems/networks in the PFC is that their function may be to *select* the material or information required for the task at hand, whereas areas in the posterior, sensory areas of the brain are involved in the actual *active maintenance* of that material or information while it is being used in a given task (see Curtis & D'Esposito (2003) and Wager & Smith (2003) for reviews). The concurrent activation of PFC and sensory cortices during executive cognitive functions has been described as 'reverberating re-entry' by Fuster, with the networks involved in a *perception-action cycle* (Figure 12.14) (Fuster, 2008).

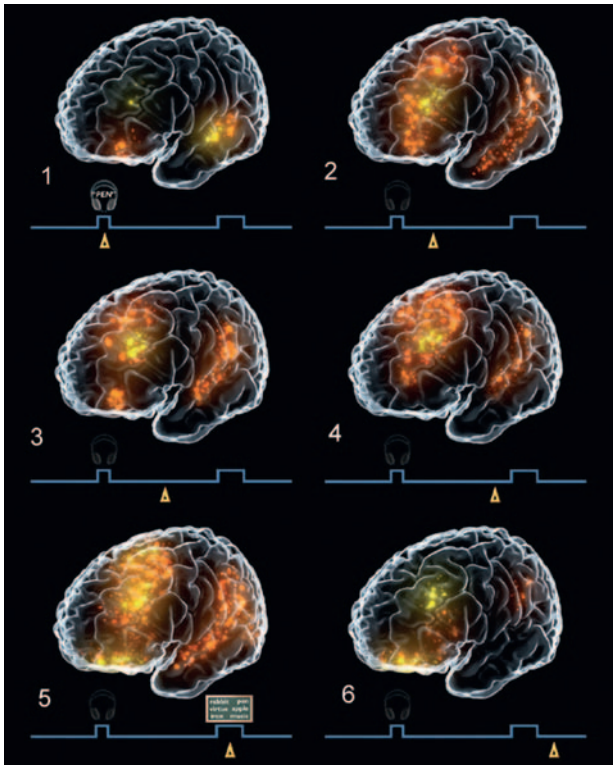


FIGURE 12.13 Cortical activation at six moments in time (yellow triangle) in the course of a verbal memory task: The memorandum, in 1, is a word through earphones. Activations of convexity cortex in orange, of medial or sulcal cortex in yellow. (1) At the cue-memorandum, the activation is restricted to auditory cortex, superior temporal gyrus, and inferior frontal cortex; (2) in early delay, it extends to lateral prefrontal, anterior cingulate, and superior-temporal and parietal association cortex; (3) in mid-delay, it persists in prefrontal and temporo-parietal cortex; (4) in late delay, it persists in prefrontal and migrates to premotor areas, while persisting in temporo-parietal cortex; (5) at the response (signaling whether cue word is on the screen), it covers visual and temporo-parietal cortex in the back, and extends to frontal eye fields, supplementary motor area (SMA), inferior frontal and orbitofrontal cortex in the front; (6) after the trial, activation lingers in anterior cingulate, orbitofrontal cortex, and language areas. *Source*: Fuster, 2008.

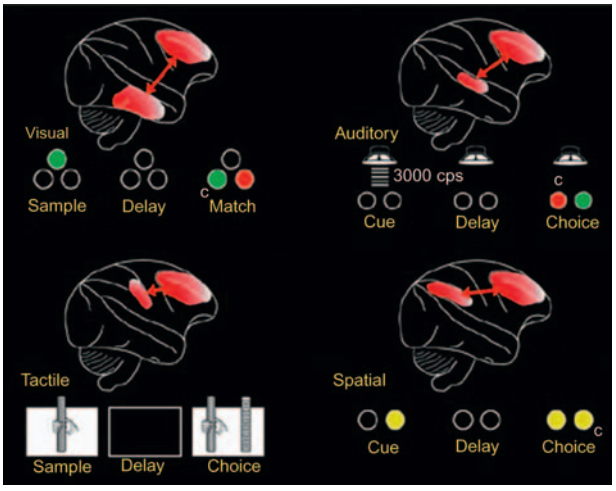


FIGURE 12.14 Schematic diagrams of a monkey's brain showing cortical areas of reciprocal interaction during working memory at the top of the perception-action cycle. The prefrontal cortex interacts by reverberation with a different posterior cortical area depending on the modality of the memorandum (sample or cue) in the four working memory tasks depicted under the diagrams. *Source*: Fuster, 2008.

6.3 Executive function and motor control

We have described a central function of the PFC as the ability to plan our actions – whether mental or physical – and then to follow out that plan. The mental planning of motor action – from initial abstract representations to the actual motor codes – takes place in the frontal lobes. A current view of the neural organization for these processes is that the more abstract representations/planning activities occur in the anterior portions of PFC, moving more posterior (and thus closer to the motor regions) as the activities become less abstract and move toward motor codes for movement (for a review, see Fuster, 2008). The level of brain activity for planning and executing complex behaviors corresponds to the level of difficulty of the action. A task frequently used to test frontal lobe executive function is the Tower of London task (Figure 12.15; Shallice, 1982). This task is like a puzzle with many steps for successful completion. In order to solve it, the subject needs to develop a plan. Researchers have found activation in DLPFC in the left hemisphere when solving this task, with higher levels of DLPFC activation found for subjects who found the task challenging (Morris *et al.*, 1993).

However, learning and practice change this effect, with well-learned – though complex – behaviors producing lower levels of brain activity (Figure 12.16) (Poldrack *et al.*, 2005; Posner & Raichle, 1994). Highly automatic behaviors like tying your shoe or locking a door produce little PFC activation. Thus, the *feeling* you may have that these behaviors are easy, requiring little effort on your part, corresponds to brain studies showing little *PFC activation* for them.

We have briefly discussed the anterior cingulated cortex (ACC) (Brodmann area 24 in Figure 12.3). What is the role of the ACC in executive function? Although the role of the ACC in executive functions is still being elucidated, one hypothesis is that it has an inhibitory effect on frontal lobe processes. If this is the case, then the ACC may represent a functional part of the orbito-medial PFC that helps in reducing the effects of

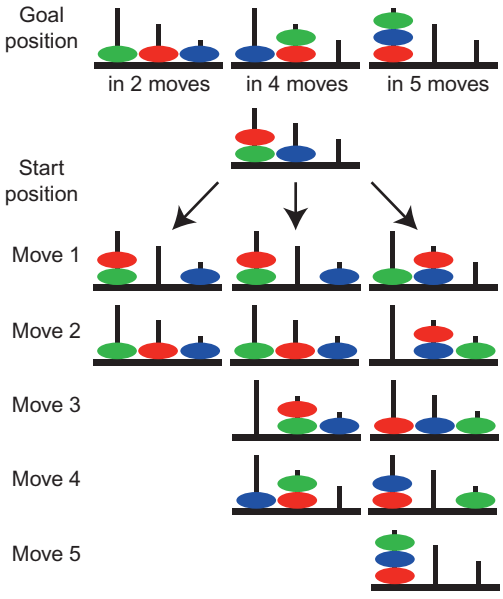


FIGURE 12.15 The Tower of London test. *Source*: Fuster, 2008.

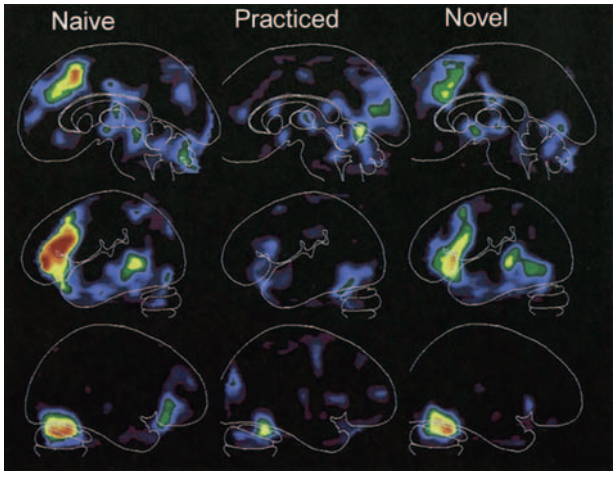


FIGURE 12.16 PET activation during performance of a verb-generation task. The subject is given a series of nouns by the investigator and required to produce a verb appropriate to each. The control task was simply the reading aloud of the names as they appeared on a TV monitor. Subtractive scans of three brain slices in three different conditions (*left to right*): performance by naive subject, subject practiced with the same list of nouns, and subject presented with a new list of nouns. *Source*: Fuster, 2008, from Posner and Raichle (1994), with permission.

distracting influences on the executive planning function (Figure 12.17; Bush *et al*., 2000). Fuster (2008) hypothesizes that this inhibitory control that resists distracting influences may serve as the flip side of executive attentional processes. Thus, in this way your success at focusing on a task at hand is aided both by your ability to pay attention to it and by your ability to ignore distractions.

6.4 Decision-making

In our everyday life, we encounter two types of situations that require two different ways to address them. Situations like balancing a checkbook and remembering a phone number or a name are *deterministic*. Each of them has a single correct solution intrinsic in the situation, all the other responses being false. By finding the correct solution, we engage in *veridical decision-making*. Situations like deciding what to wear, which movie to see, or which career path to choose are *ambiguous*. They do not have an intrinsically correct solution. By making our choice, we engage in *adaptive* (or *actor-centered*) *decision-making*.

In school, we are given a problem and must find the correct answer. Only one correct answer usually exists. But aside from high school exams, college tests, and factual and computational trivia, most decisions we make in our everyday lives do not have intrinsically correct solutions. The choices we make are not inherent in the situations at hand. They are a complex interplay between the properties of the situations and our own properties, our aspirations, our doubts, and our histories. The prefrontal cortex is central to such decision-making. Finding solutions for deterministic situations often is accomplished algorithmically. It increasingly is delegated to various devices: calculators, computers, directories of all kinds, but making choices in the absence of inherently correct solutions remains, at least for now, a uniquely human territory. In a sense, the freedom of choice is possible only when ambiguity is present.

Resolving ambiguity often means choosing the question first, that is, reducing the situation to a question that does have a single correct answer. Precisely how we disambiguate the situation depends on our priorities at the moment, which themselves may change depending on the context. An inability to reduce ambiguity leads to vacillating, uncertain, inconsistent behavior.

At the same time, an individual must have the flexibility to adopt different perspectives on the same situation at different times. The organism must be able to disambiguate the same situation in a multiple of different ways and to have the capacity to switch between them at will. Dealing with inherent ambiguity is among the foremost functions of the frontal lobes. Studies have shown that patients with frontal-lobe damage approach inherently ambiguous situations differently from the way healthy people do. The loss of the ability to make decisions is among the most common signs of early dementia. Damage to other parts of the brain does not seem to affect these processes.

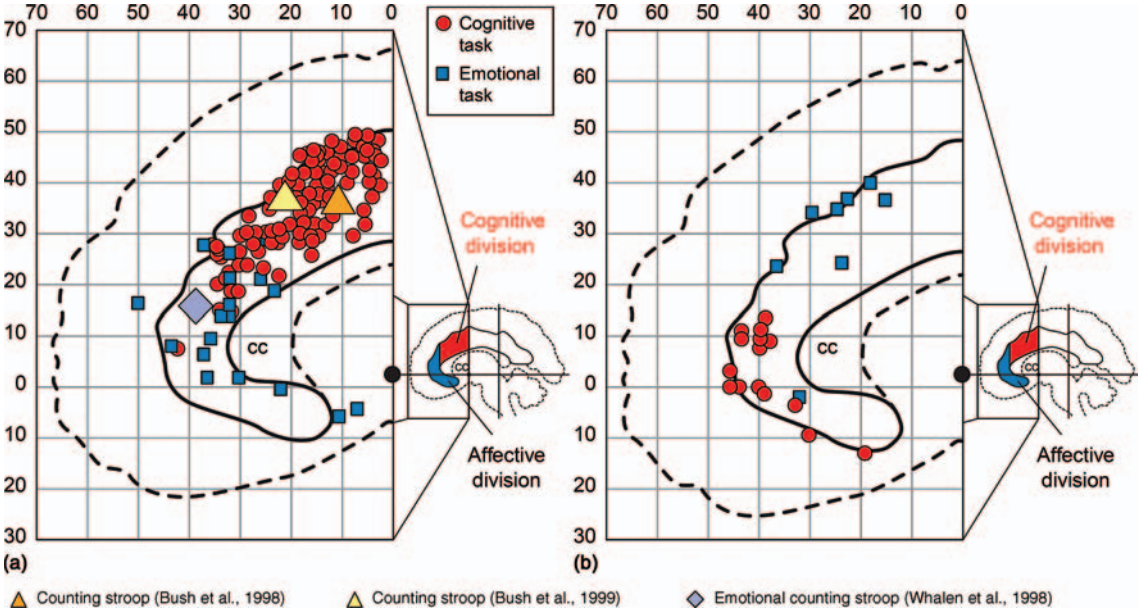


FIGURE 12.17 Confirming separate cognitive and emotional conflict regions. A summary of many studies of the anterior cingulate cortex, showing different cognitive and emotional regions. *Source*: Bush *et al*., 2000.

Where do the processes underlying decision-making occur in the frontal lobes? Converging evidence implicates the orbito-medial PFC, especially when there are emotional factors in the decision-making process. Think about playing a hand of poker. You must constantly make decisions about what to do next with incomplete information – should you fold, raise . . . what will your competitors do? In order to do well at this game, you need to assess the risk factors and the rewards. Bechara and colleagues have investigated these processes using the Iowa gambling task (Bechara, Damasio, Tranel, & Anderson, 1994). They and many other researchers investigating the neural bases for assessing risk and reward have shown that the orbital or medial PFC is activated during these tasks.

Have you ever been in a state of internal conflict over a decision that you are making? With a real sense that 'part of you' wants you to listen to your *heart* and another 'part of you' wants you to listen to your *head*? This type of internal conflict between emotional feelings and rational thoughts is proposed to reflect the trading relationship between the orbito-medial PFC, with its connections to subcortical emotional regions, and lateral PFC, with its connections to executive control regions.

6.5 Rule adoption

In order to navigate our way through our complex daily lives, it is critical to develop ways to short-cut all the things that we need to plan for and carry out. Humans are wonderful rule adopters – we develop and learn strategies for streamlining our busy lives. Like a strategic plan or a schema, rules help us increase our efficiency. The Wisconsin Card Sorting test (shown in Figure 12.18) is a good example of the

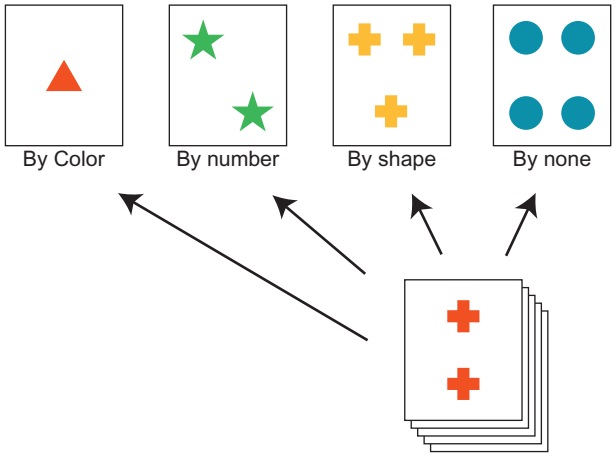


FIGURE 12.18 The Wisconsin Card Sorting Test (WCST). The cards can be sorted by matching the color of the item on the card, or the number of items, their shape, or even if they don't match on any of these features. At the beginning of the game, the experimenter determines which matching 'rule' to be used (such as 'match the new card by color') but he does not tell the player the rule – the player must learn it by trial and error. During the game, the experimenter will change the rule and again, the player must learn the new rule through trial and error. This is a test of mental flexibility: the ability to learn a new rule and to adapt to a new rule when needed. *Source*: Fuster, 2008.

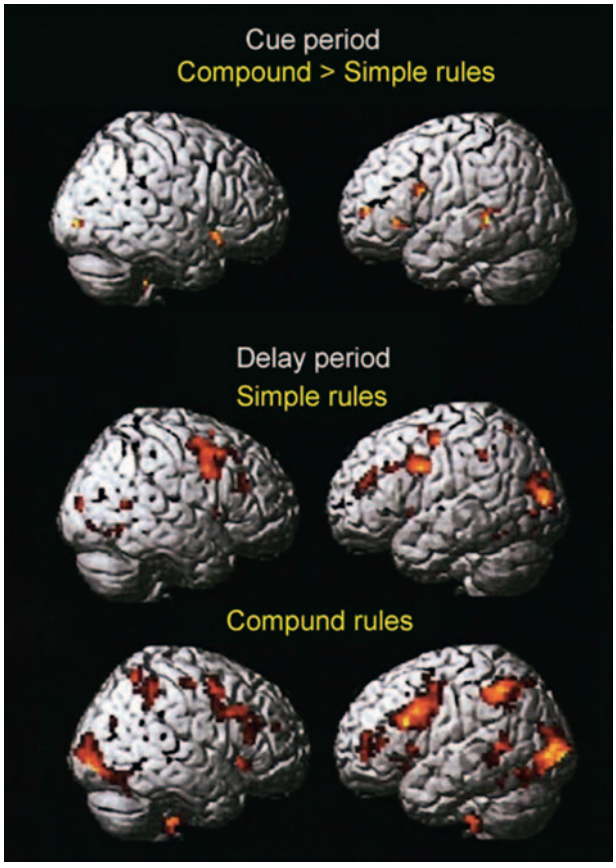


FIGURE 12.19 In this study, the experimenters wanted to see which brain areas were active while subjects implemented either simple or compound abstract 'rules'. A rule cue was provided followed by a long (7–15 s) delay. Brain areas more active for compound versus simple cues are shown at the top of this figure. Areas active during the delay (while the subject is keeping the rule in mind) are shown in the middle (simple rule) and bottom (compound rule) of the figure. *Source*: Bunge, 2004, as adapted in Fuster, 2008.

mental flexibility humans have in acquiring rules and, importantly, in changing them when needed.

Neuroimaging studies of rule learning in PFC have shown that, in a manner similar to attentional and working memory demands, neural activity in the frontal regions increases with the complexity of the rule set to be learned or carried out (Figure 12.19; Bunge, 2004).

Neuroimaging studies have shed new light on the many and diverse operations carried out – or directed – by the PFC, from paying attention to a stimulus in your environment, to monitoring how it is changing, to keeping something in mind, to complex decision-making. Many of these processes are highly overlapping in time and neural regions, thus we are still elucidating which frontal lobe areas contribute to these processes. Although we are still in the early stages of understanding just how and where executive processes are being done in the PFC, converging evidence from neuroimaging studies are beginning to present a clearer picture of PFC function.

7.0 FRONTAL LOBE DYSFUNCTION

We have discussed many functions of the frontal lobe including voluntary attention, working memory, decision making, and even your personality. What happens when this critical area of the brain is damaged? Or fails to develop in a typical manner? The answers to these questions are as complex as the frontal lobes themselves.

7.1 The fragile frontal lobes

Frontal lobe dysfunction often reflects more than direct damage to the frontal lobes (Goldberg, 1992). The frontal lobes seem to be the bottleneck, the point of convergence of the effects of damage virtually anywhere in the brain. There is a reciprocal relationship between frontal and other brain injuries. Damage to the frontal lobes produces wide ripple effects through the whole brain. At the same time, damage anywhere in the brain sets off ripple effects interfering with frontal lobe function. This unique feature of the frontal lobes reflects its role as the 'traffic hub' of the nervous system, with a singularly rich set of connections to and from other brain structures. This makes frontal lobe dysfunction the most common and least specific finding among neurological, psychiatric, and neurodevelopmental conditions (Goldberg, 1992).

The frontal lobes' exceptionally low 'functional breakdown threshold' is consistent with Hughlings Jackson's concept of 'evolution and dissolution' (1884). According to Jackson's proposal, the phylogenetically (evolutionary) youngest brain structures are the first to succumb to brain disease. The frontal lobes' unique vulnerability is probably the flip side of the exceptional richness of their connections. A frontal lobe dysfunction does not always signify a direct frontal lobe *lesion*. Instead, it may be a remote effect of a diffuse, distributed, or distant lesion.

7.2 Frontal lobe syndromes

The importance of executive functions can be best appreciated through the analysis of their disintegration following brain damage. A patient with damaged frontal lobes retains, at least to a certain degree, the ability to exercise most cognitive skills in isolation (Luria, 1966). Basic abilities such as reading, writing,

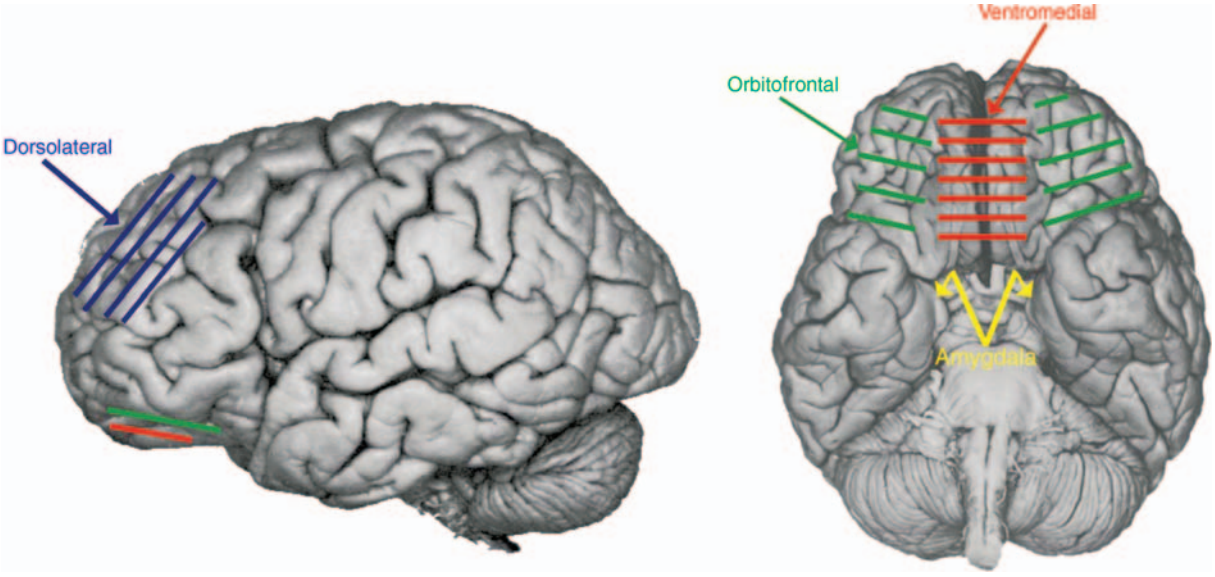


FIGURE 12.20 The orbitofrontal region is just above the orbits of the eyes. The orbitofrontal cortex (green stripes) can be distinguished in the ventral prefrontal lobe. Orbitofrontal cortex is involved in understanding future rewards, changes in reward contingencies, and goal selection. Damage to the orbitofrontal region may lead to a loss of behavioral inhibition. *Source*: Davidson and Irwin, 1999.

simple computations, verbal expression, and movements may remain largely unimpaired. Deceptively, the patient will perform well on the psychological tests measuring these functions in isolation. However, any synthetic activity requiring the coordination of many cognitive skills into a coherent, goal-directed process will become severely impaired.

Damage to different parts of the frontal lobes produces distinct, clinically different syndromes. The most common among them are the *dorsolateral* and *orbitofrontal prefrontal syndromes* (Figure 12.20; Goldberg and Costa, 1985).

7.2.1 Dorsolateral prefrontal syndromes

Most common symptoms of dorsolateral prefrontal syndromes are *personality changes*, *field-dependent behavior*, and *perseverative behavior*.

Personality changes

Clinically, a patient with dorsolateral frontal syndrome will be characterized by impaired ability to initiate behaviors. He or she tends to show 'flat affect'; that is, monotonous speech and sense of indifference. The patient is neither sad nor happy; in a sense, he or she has no mood. This state of indifference persists no matter what happens to the patient, good things or bad. However, the most conspicuous feature of a patient with dorsolateral syndrome is a drastically impaired ability to initiate behaviors. Once started in a behavior, however, the patient is equally unable to terminate or change it on his or her own. Such combined 'inertia of initiation and termination' is seen in various disorders affecting the frontal lobes, including chronic schizophrenia.

Following even relatively mild head trauma, it is common for patients to become indifferent and devoid of initiative and drive. The change may be subtle, and it is not always apparent to family members or even physicians that the change is neurological in nature, that it is a mild form of the frontal lobe syndrome. These symptoms are often called personality change, but personality is determined to a large extent by neurobiology. The frontal lobes have more to do with our personalities than any other part of the brain, and frontal lobe damage can produce profound personality change.

Field-dependent behavior

Another common symptom of dorsolateral prefrontal syndromes is that the patient is at the mercy of incidental distractions and thus is unable to follow internally generated plans. In extreme cases it may take the form of field-dependent behavior. A frontal lobe patient will drink from an empty cup, put on a jacket belonging to someone else, or scribble with a pencil on the table surface, merely because the cup, the jacket, and the pencil are there, even though these actions make no sense. This phenomenon was studied extensively by the French neurologist Francois Lhermitte,

who called it *utilization behavior* (Lhermitte, 1983). In the most extreme cases, field-dependent behavior takes the form of direct imitation, called *echolalia* (imitation of speech) or *echopraxia* (imitation of action).

Such patients will perform particularly poorly (Stuss *et al*., 2001) on the *Stroop Test* (Stroop, 1935). What makes the Stroop Test so interesting? It requires that we go against our immediate impulse. The impulse is to read the words; this is the natural tendency of every literate person when you see written material. But the task is to name the colors. To complete the task successfully, we must follow the internal plan, the task, *against our natural, entrenched tendency* (see also Chapters 2 and 8).

When neurological illness affects the frontal lobes, the ability to stay on track often becomes lost, and the patient is often at the mercy of incidental environmental stimuli and tangential internal associations. Easy distractibility is a feature of many neurological and psychiatric disorders, and it is usually associated with frontal lobe dysfunction. For example, *attention deficit hyperactivity disorder (ADHD)*, with its extreme distractibility, is usually linked to frontal lobe dysfunction (Barkley, 1997). The relationship between the frontal lobes' role in guiding behavior by internal representation during performance on Stroop Test, ADHD, and emotional valence of a task was elucidated in a combined analysis of multiple studies (Figure 12.17).

Mental rigidity and perseveration

Our ability to maintain mental stability has to be balanced by *mental flexibility*. No matter how focused we are on an activity or a thought, there comes a time when the situation calls for doing something else. Being able to change one's mindset is as important as staying mentally on track. The capacity to switch with ease from one activity or idea to another is so natural and automatic, that we take it for granted. In fact, it requires complex neural machinery, which also depends on the frontal lobes. Mental flexibility, the ability to see things in a new light, creativity, and originality all depend on the frontal lobes. More profound forms of mental rigidity produce *obsessive-compulsive disorder* (OCD), in which dysfunction of the caudate nuclei closely linked to the frontal lobes has been implicated (Rauch *et al*., 1994).

Frontal lobe damage often produces extreme mental rigidity, which may severely undermine the patient's cognition. Quite often a closer look at a frontal patient's performance on a number of tasks shows that complete transition from one task to another is impossible, and fragments of a previous task attach themselves to the new one. This phenomenon is called *perseveration.*

A seemingly simple neuropsychological test is quite sensitive to subtle impairment of mental flexibility. The test, known as the Wisconsin Card Sorting Test (Grant and Berg, 1948), requires the subject to sort cards with simple geometric forms into three categories according to a simple principle (Figure 12.18). The classification principle is not revealed in advance and the subject must establish it through trial and error. But when the principle finally has been mastered it abruptly changes unbeknownst to the subject. Once the subject catches up with the new principle, the principle is changed without forewarning again, and again, and again. The task requires planning, guidance by internal representation, mental flexibility, and working memory – in short all the aspects of frontal lobe function that we have discussed.

7.2.2 Orbitofrontal prefrontal syndromes and self-control

The *orbitofrontal prefrontal syndrome* is, in many ways, the opposite of the dorsolateral syndrome. The patients are behaviorally and emotionally *disinhibited*. Their affect is rarely neutral, constantly oscillating between euphoria and rage, with impulse control ranging from poor to nonexistent. Their ability to inhibit the urge for instant gratification is severely impaired. They do what they feel like doing, when they feel like doing it, without any concern for social taboos and legal prohibitions. They have no foresight of the consequences of their actions. A patient afflicted with the orbitofrontal syndrome (due to head injury, cerebrovascular illness, or dementia) may engage in shoplifting, sexually aggressive behavior, reckless driving or other actions commonly perceived as antisocial. These patients are known to be selfish, boastful, puerile, profane, and sexually explicit. Their humor is off-color and their jocularity, known as *Witzelsucht*, resembles that of a drunken adolescent (Oppenheim, 1889). If the dorsolateral patients are in a sense devoid of personality, then orbitofrontal patients are conspicuous for their 'immature' personality.

7.2.3 Reticulofrontal disconnection syndrome

In cases when the frontal lobes themselves are structurally intact but the patient presents with frontal lobe symptoms, the problem may lie with the pathways connecting frontal lobes to some other structures.

Damage to these pathways may result in a condition known as the *reticulofrontal disconnection syndrome* (Goldberg *et al*., 1989).

The brainstem contains the nuclei thought to be responsible for the arousal and activation of the rest of the brain. A complex relationship exists between the frontal lobes and the brainstem reticular nuclei, which are in charge of activation and arousal. The relationship is best described as a loop. On the one hand, the arousal of the frontal lobes depends on the ascending pathways. On the other hand, there are pathways projecting from the frontal lobes to the reticular nuclei of the ventral brainstem. Through these pathways the frontal lobes exert their control over the diverse brain structures by modulating their arousal level. If the frontal lobes are the decision-making device, then the brainstem structures in question are an amplifier helping communicate these decisions to the rest of the brain in a loud and clear voice. The descending pathways are the cables through which the instructions flow from the frontal lobes to the critical ventral brainstem nuclei.

We can easily see how damage to the pathways between the brainstem and the frontal lobes may disable executive functions without actually damaging the frontal lobes *per se*.

7.3 Frontal lobe damage and asocial behavior

The relationship between frontal lobe damage and asocial behavior is particularly intriguing and complex. It has been suggested, based on several published studies, that the prevalence of head injury is much higher among criminals than in the general population, and in violent criminals than in nonviolent criminals (Volavka *et al*., 1995; Raine *et al*., 1997). For reasons of brain and skull anatomy, closed head injury is particularly likely to affect the frontal lobes directly, especially the orbitofrontal cortex. Furthermore, damage to the upper brainstem is extremely common in closed head injury, even in seemingly mild cases, and it is likely to produce frontal lobe dysfunction even in the absence of direct damage to the frontal lobes by producing the 'reticulofrontal disconnection syndrome' (Goldberg *et al*., 1989).

Adrian Raine and his colleagues (Raine *et al*., 1997) studied the brains of convicted murderers with PET scans and found abnormalities in the PFC. Raine and colleagues (2000) also studied the brains of men with antisocial personality disorder and found an 11% reduction in the gray matter of their frontal lobes. The cause of this reduction is uncertain, but Raine believes that this reduction is at least in part congenital, as opposed to caused by environmental factors such as abuse or bad parenting. The link between frontal lobe dysfunction and asocial behavior raises an important set of social, moral, and legal issues far beyond the scope of this chapter.

7.4 Other clinical conditions associated with frontal lobe damage

PFC is afflicted in a wide range of conditions (Goldberg, 1992; Goldberg and Bougakov, 2000) and it is not necessary to have a focal frontal lesion to have prefrontal dysfunction. The frontal lobes are particularly vulnerable in numerous nonfocal conditions. Such disorders as schizophrenia (Ingvar and Franzen, 1974; Franzen and Ingvar, 1975), traumatic brain injury (TBI) (Deutsch and Eisenberg, 1987), Tourette's syndrome (Tourette, 1885; Shapiro and Shapiro, 1974; Sacks, 1992), and attention deficit (hyperactivity) disorder (AD(H)D) (Barkley, 1997) are known to involve frontal lobe dysfunction. In TBI, for instance, the frontal lobe dysfunction can be caused by either direct frontal injury, or by injury disrupting the brainstem-frontal connection (Goldberg *et al*., 1989). Executive functions are also compromised in dementia and in depression.

It appears that it is not necessary to have a frontal lobe lesion to have frontal lobe syndrome. There are many conditions where, based on functional neuroimaging and neuropsychological studies, frontal lobe dysfunction is present, but there is no evidence of structural morphological damage to the frontal lobes.

Attention deficit (hyperactivity) disorder (AD(H)D)

The prefrontal cortex and its connections to the ventral brainstem play a particularly important role in the mechanisms of attention. When we talk about the attention deficit (hyperactivity) disorder (AD(H)D), we usually implicate these systems. The exact causes of damage to these systems vary. They may be inherited or acquired early in life. They may be biochemical or structural. As we already know, frontal lobes are particularly vulnerable in a very broad range of disorders, hence the very high rate of frontal lobe dysfunction. The way the diagnosis of AD(H)D is commonly made, it refers to any condition characterized by mild dysfunction of the frontal lobes and related pathways in the absence of any other, comparably

severe dysfunction. Given the high rate of frontal lobe dysfunction due to a variety of causes, the prevalence of genuine AD(H)D should be expected to be very high.

To understand better the proposed mechanism of AD(H)D we need to understand the nature of another aspect of executive control – selective attention. The goal of action must be identified and it must effectively guide behavior for a period of time. We already know that goal-setting and goal-maintenance are provided by the *prefrontal cortex*. The prefrontal cortex exerts its influence on the posterior aspects of the cortical hemispheres. These are the structures most directly involved in processing the incoming information. Depending on the goal at hand, distinct, particular parts of the posterior cortex must be brought into the state of optimal activation. The selection of these areas is accomplished by the prefrontal cortex. The prefrontal cortex exerts its influence through the nuclei of the *ventral brainstem*, which can selectively activate vast cortical regions through their ascending projections. The prefrontal cortex guides the influence of these nuclei on the posterior cortices through its own descending pathways into the ventral brainstem. Finally, the prefrontal cortex *modifies* its control over brainstem nuclei, based on the *feedback* it receives from the posterior cortex.

In sum, attention can best be described as a loop-like process involving complex interactions between the *prefrontal cortex*, *ventral brainstem* (and possibly also *nonspecific midline thalamic nuclei*), and *posterior cortex* (Figure 12.21). Breakdown anywhere along this loop may interfere with attention, thus producing a form of attention deficit disorder. Therefore, any damage to the prefrontal cortex or its pathways may result in attentional impairment.

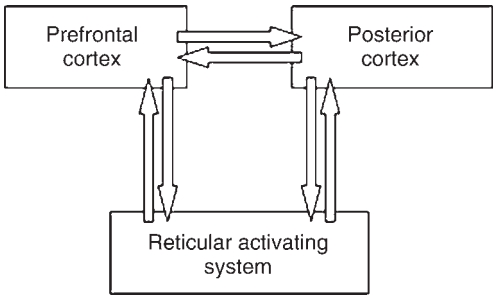


FIGURE 12.21 An attentional loop combining frontal, brainstem, and posterior cortex. Goldberg (2001) proposed that attentional functions may be influenced not just by the frontal lobes, but by a causal loop extending downward into the reticular formation of the brainstem, going upward to posterior cortex. This view is consistent with evidence regarding the brainstem arousal system. *Source*: Elkhonon Goldberg, with permission.

8.0 A CURRENT VIEW OF ORGANIZING PRINCIPLES OF THE FRONTAL LOBES

After decades of research into frontal lobe function in nonhuman primate and in human, using many experimental techniques and methods, some organizing principles have emerged. A leader in the field of frontal lobe research is Joaquin Fuster, who proposed a model for frontal lobes function. He states:

1. The entirety of the cortex of the frontal lobe is devoted to the representation and production of action at all levels of biological complexity
2. The neuronal substrate for the production of any action is identical to the substrate for its representation
3. That substrate is organized hierarchically, with the most elementary actions at low levels of the hierarchy, in orbitofrontal and motor cortex, and the most complex and abstract actions in lateral prefrontal cortex
4. Frontal-lobe functions are also organized hierarchically, with simpler functions nested within, and serving, more global functions. (Fuster, 2008, page 334.)

The notion of a hierarchical organization for simple versus complex, abstract versus concrete frontal lobe function has been developed in neuroimaging studies of human frontal lobe processes. A recent review article by Badre (2008) provided a summary of findings to date, including models developed by Koechlin, D'Esposito, and others, showing data supporting the view of a hierarchal organization of the frontal lobe, with an anterior-to-posterior organization that is based on the degree of abstraction (Figure 12.22).

Neuroimaging Summary

While many more details clearly need to be discovered before we have a unitary explanation of frontal lobe function, recent advances in neuroimaging techniques and methods have helped to increase our knowledge of the complex role the frontal lobes, and in particular the PFC, play in human cognition. However, even though neuroimaging studies may serve to guide us as to specific regions where certain executive processes – such as voluntary attention or working memory – may be located, they show a dramatically different picture of human executive function than is seen when observing a patient with frontal lobe damage. How do results from neuroimaging studies correspond to

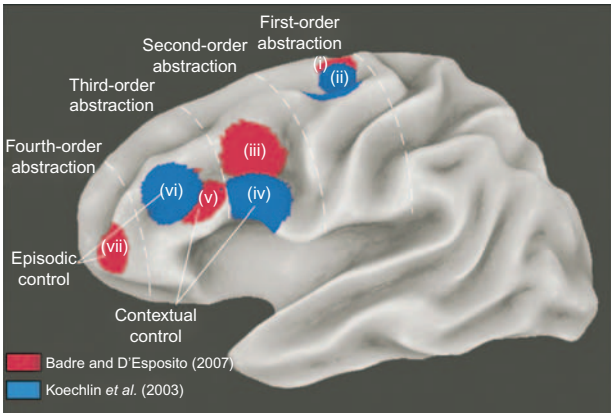


FIGURE 12.22 Results from the response, feature, dimension, and context experiments and comparison to the model of Koechlin *et al*. (2003). Abstract relational hierarchy seems to provide a parsimonious account of rostro-caudal gradient across the models of Koechlin *et al*. (2003) and Badre and D'Esposito (2007). Spheres with diameters of 8 mm (within the smoothing kernel of each experiment) were centered on maxima from response (i), feature (iii), dimension (v), and context (vi) manipulations of Badre and D'Esposito (2007) (red), and on the sensory (ii), context (iv), and episodic (vi) manipulations of Koechlin *et al*. (2003) (blue). These spheres were rendered on an inflated Talairach surface. Note that the spheres are for precise illustration of proximity but do not represent actual spread of activation in each experiment. Broken lines separate manipulations at equivalent levels of abstraction in a representational hierarchy. Equivalent episodic and contextual control manipulations across the two experiments are also labeled. *Source*: Badre, 2008, adapted from Badre and D'Esposito, 2007, with permission.

studies of patients with frontal lobe syndromes? These two sets of findings are not easy to bring together into a cohesive whole at present. Neuroimaging studies have provided a wealth of data about specific regions and locations that activate for various aspects of frontal lobe processes but the results don't correspond directly to what we know about human behavior when frontal lobes are damaged. This is the challenge for cognitive neuroscientists – to continue to provide converging evidence across many techniques and subject groups in order to elucidate the underlying organizational principles for the complex and uniquely human PFC, the 'organ of civilization'.

9.0 TOWARD A UNIFIED THEORY OF EXECUTIVE CONTROL: A CONCLUSION

To summarize, after having been overlooked for many decades, executive functions have become the focus of an ever-increasing body of research.

Early neuroimaging studies of frontal lobe functions produced a complex patchwork of regions specialized for sensory modalities, linguistic versus nonlinguistic processes, object-oriented versus spatially-oriented, and 'what' versus 'where' pathways. The early approach of elucidating capsulated 'modules' for the PFC produced many important findings but ultimately did not provide a clear picture of the organizational principles for the PFC, nor did they correspond well with the wealth of information about frontal lobe syndromes.

A very different approach traces its lineage to the work by the great Russian neuropsychologist Alexander Luria (1966). A continuation and extension of Luria's original theory can be seen in the relatively recent trend toward the refutation of the modular view of functional neocortical organization in favor of the distributed-emergent principle of functional cortical organization (Goldberg *et al*., 1989; Goldberg, 1992; Fuster, 2003). According to Goldberg's gradiental theory, the functional organization of heteromodal association cortices (such as prefrontal cortices) is interactive and distributed. The heteromodal association cortex develops along the continuous distributions. In these distributions (called gradients) functionally close aspects of cognition are represented in anatomically close areas of the association neocortex.

Yet another theory of cortical representation elaborating on Luria's functional systems theory was put forth by Joaquin Fuster (2003). Fuster maintains that cognitive functions do not have discrete cortical representation. In his theory, he introduces a reentrant unit, called *cognit*, which he proposes as a generic term for any representation of knowledge in the cerebral cortex. Cognits are dynamic structures which, in neural terms, roughly coincide with neuronal assemblies and the connections between the neurons. According to Fuster, cognitive functions are represented by information exchange within and between cognits, and different cognitive functions draw upon many overlapping cognits. The crucial tenet of Fuster's theory is that different cognits (neural networks) have identifiable cortical distribution but cognitive functions that use them do not, since different functions may rely on the same or similar circuits.

According to these theories, the nature of cortical representation of executive control is distributed as well as localized. Executive control can be considered unitary in the sense that it is in charge of actions, both external and internal, and works to integrate such factors as time, novelty, complexity, and possibly ambiguity.

10.0 DRAWING EXERCISES AND STUDY QUESTIONS

1 What are some of the functions attributed to the prefrontal lobe?
2 Discuss a current debate about the specificity of prefrontal functions.
3 In the outline brain shown in Figure 12.23:
   a. Color the major lobes
   b. Label major landmarks, like the central sulcus and Sylvian fissure.
   c. Label the major gyri (green lines) and sulci (dotted red lines).

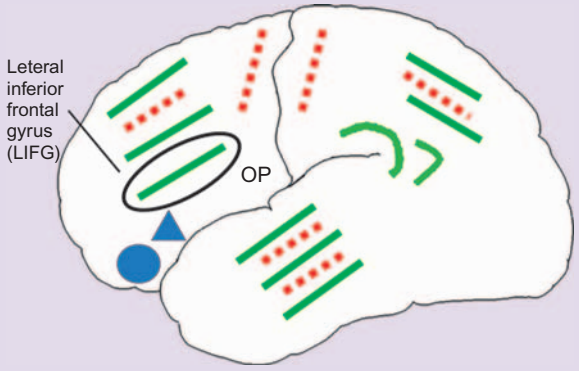
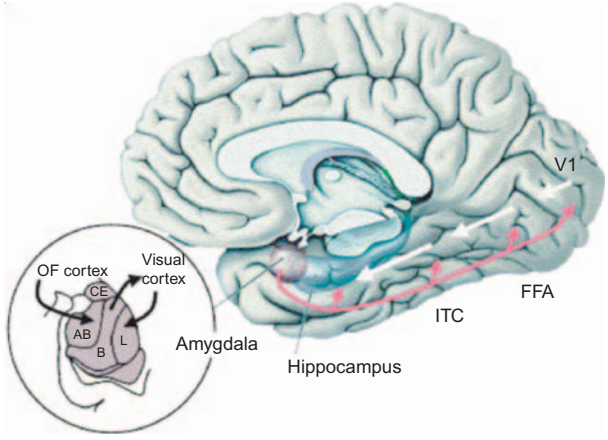
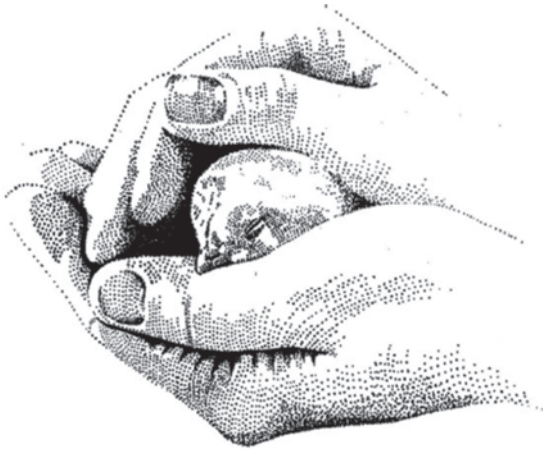


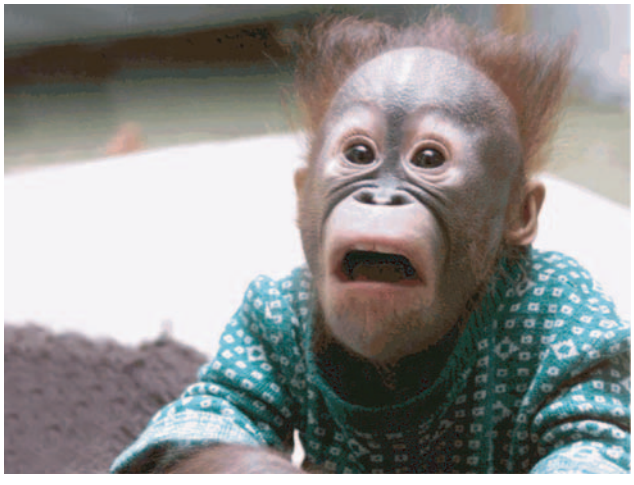
FIGURE 12.23

For Charles Darwin, it was obvious beyond any need for argument that non-human animals are sentient '. . . the lower animals, like man', he wrote in 1871, 'manifestly feel pleasure and pain, happiness and misery' (p. 39). 'The fact that the lower animals are excited by the same emotions as ourselves is so well established that it will not be necessary to weary the reader by many details' (However,) . . . in the belief that identifying problems and finding ways to answer them is a way to move forwards, I shall first emphasize why sentience is still a profound problem, despite the ease with which Darwin spoke about the mental experiences of animals.

Marian Stamp Dawkins (2006)







The basic emotional brain is highly conserved among mammals, and possibly even more widely. Upper left, a human brain seen from the midline (medially), showing how information can flow from visual cortex (V1) to the amygdala, an emotional 'hub' for neuronal traffic from many different sources. Snakes appear to be a biological stimulus for fear for both humans and other mammals. On the opposite pole, cradling young birds and other newborns seems to evoke a soothing and calming effect (Panksepp, 1998). Obviously humans have a giant neocortex, which modifies basic mammalian emotional systems centered in the limbic (core) brain.

CHAPTER

13

Emotion

OUTLINE

1.0 INTRODUCTION

Do you remember where you were on the morning of September 11, 2001? You likely do recall that day, and you probably do not have a strong memory for, say, September 9 of that year. Why is this? The events of 9/11 are firmly etched in our brains because of the highly charged emotions that are entwined with the memory of the occurrences of that day. In previous chapters, we have discussed higher cognitive brain functions such as memory, executive functions, and language. Our emotions are strongly coupled with the brain systems underlying these cognitive functions. In this chapter, we will explore the emotion systems of the brain and their interactions with cognitive processing. The term 'affective neuroscience' was coined in the late 1990s to denote a new area of study: the neuroscience of emotion. While a great deal is now known about emotion in the brain, we will focus here on how emotion systems shape and influence cognitive processes.

1.1 The triune brain

Paul MacLean introduced the 'triune brain' concept in the 1960s to describe the functionally distinct layers of the mammalian brain. It has become a widely used way of thinking about the overall functional

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

organization of the brain. While some aspects of the triune brain theory have been controversial, nevertheless, it remains a helpful way to think about different 'layers' of the mammalian brain. In MacLean's view, the brain developed over the course of vertebrate evolution into a three-layered organ, where these layers retain some of the separateness of their different evolutionary origins despite being highly interconnected. We can see the effects of each of the layers in human behavior, especially in the relationship of cognition and emotion.

The oldest layer of the brain is called the *reptilian brain*. It is composed of the brainstem (medulla, pons, cerebellum, midbrain, globus pallidus, and olfactory bulbs) – the structures that dominate in the brains of snakes and lizards. This brain layer does not learn very well from experience but is inclined to repeat instinctual behaviors over and over in a fixed way. In humans, this part of the brain controls survival activities like breathing, heart rate, and balance. We will not have much to say about the reptilian brain in this chapter.

The *mammalian brain* is layered over the reptilian brain (Figure 13.1). It consists primarily of a system of brain parts called the *limbic system*. The word 'limbic' comes from the Latin word *limbus* and means 'border, edge, or hem' – it refers to the location inside the cerebral hemispheres around the edge of the lateral ventricles (fluid-filled spaces). The limbic system was first recognized in the late 1800s, but an understanding of its function in emotion did not develop until the work of neuroanatomist Papez was published in 1937. Another older name for the limbic system is the Papez circuit.

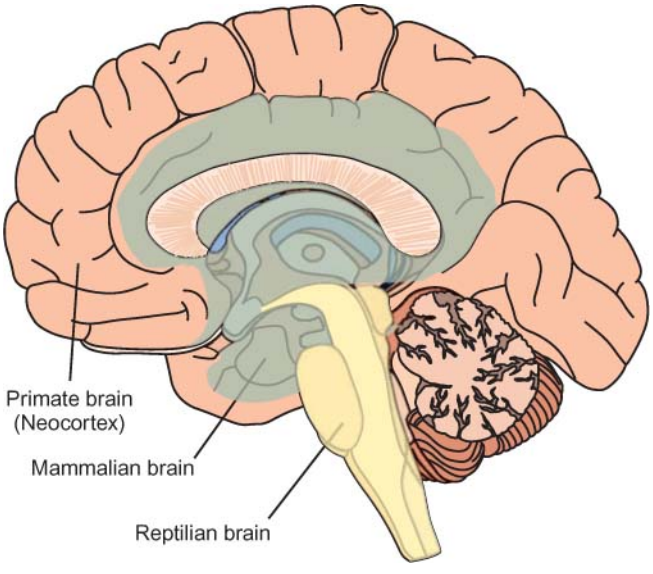


FIGURE 13.1 The triune brain: orange represents neocortex, green is the mammalian brain, and yellow is the reptilian brain.

The list of component parts of the limbic system varies depending on the researcher that we consult – there seems to be no universal agreement about what the limbic system actually consists of! Some neuroscientists think that we should no longer speak of a limbic system at all. We will retain the term as a useful organizing concept for a set of related subcortical brain parts that support our emotional life. Commonly cited constituents are the amygdala, hippocampus, parahippocampal cortex, cingulate gyrus, hypothalamus, and ventral striatum/nucleus accumbens.

The limbic system has a major role in human emotion. We see the effects of the limbic system in our conscious experience in the added valence (positive or negative value or feeling) and salience ('noticeableness') of particular images and thoughts. We share this part of our brain with other mammals. Prototypic mammalian emotional responses are easily recognizable in our pet dogs and cats.

In terms of the adaptive role of the limbic system, we can say that the limbic system contains several distinct systems evolved to respond to mammalian evolutionary pressures such as danger, reproductive and nurturance needs, and acquisition of food. For example, the amygdala and hypothalamus cooperate in an *early warning system* for danger, initiating survival maneuvers automatically when confronted with stimuli similar to those encountered in past dangerous situations. However, the amygdala's stimulus processing has low resolution of details compared to that of the sensory areas of the cerebral cortices. Stimulus recognition in the limbic system follows a 'close enough is good enough' rule, so we sometimes find ourselves jumping at the site of a long, dark coil in the grass, only to find that it is a garden hose and not a snake. Following the conditioning of evolutionary history, the limbic system would 'rather be safe than sorry'. In our conscious experience, we find ourselves acting without voluntary initiation under the influence of the amygdala. Moments later, our rational selves feel embarrassment at our apparently silly behavior. We can easily find other examples of the interplay of the limbic system and the cortical system in our everyday behavior. We will look more closely at this shortly.

The limbic system is densely interconnected with the cortex, particularly through the orbital gyri of the

VM-PFC (ventromedial prefrontal cortex) and also the insular cortex. The dense connections with the VM-PFC have led to its nickname as the *feeling part of the thinking brain*. VM-PFC is a gateway between the limbic system and neocortex.

The *neocortex* or *primate brain* is the most recent addition to our brains. It consists of the wrinkled covering of the cerebral hemispheres (as well as some subcortical nuclei, such as the basal ganglia), which has mushroomed in non-human primates and humans compared to other mammals. In humans, the neocortex is the home of our complex cognitive, linguistic, motor, sensory, and social abilities. The neocortex gives us considerable flexibility and creativity in adapting to a changeable environment. Cortex functions to socialize and control expression of emotions that originate in the limbic system; cortical appraisal of situations is also necessary for a more nuanced emotional repertoire than is possible based on the functioning of the limbic system alone.

1.2 Basic emotions and the role of reflective consciousness

Emotional responsiveness is governed by:

1. *classically conditioned responses* to stimuli that previously brought pleasure or created pain mediated by subcortical systems and
2. *cognitive appraisals* of stimuli in context mediated by neocortex.

Neuroscientists have given most attention to the classical conditioning studies conducted with animal models. Almost no attention has been given to the possibility of multiple emotional systems in the brain. To date, the origins of fear in the amygdala have received attention as the dopamine-based 'reward system'. But interest in the explanation of neural bases of the wide variety of distinctly felt emotional experiences is lacking. With the advent of increasingly fine-grained brain imaging methods, this may change.

While classical conditioning remains an important explanation of learned emotional associations, affective neuroscientists have begun to think of mammalian emotion as arising from *several separate genetically determined networks* of brain areas, each serving a particular adaptive function, each giving rise to a unique motor routine when activated, each having a unique 'calling condition' or evoking stimulus, and each being the neural substrate of distinct conscious emotional feelings. A psycho-ethological perspective allows us to see emotional functioning in an adaptive context.

2.0 PANKSEPP'S EMOTIONAL BRAIN SYSTEMS

Jaak Panksepp (1998) offered a functional definition of an emotional system in the brain (illustrated in Figure 13.2):

1. The underlying circuits are genetically predetermined to respond unconditionally to stimuli representing evolutionary pressures faced by the species
2. The circuits organize motor programs and autonomic and hormonal changes to respond to the environmental challenge or opportunity at hand
3. The circuits tune sensitivities of sensory systems to be responsive to stimuli relevant to the emotion evoked
4. The positive feedback of neural activity means emotional arousal outlasts the precipitating circumstances
5. Emotional circuits can come under cognitive control
6. Emotional circuits reciprocally influence higher decision-making and appraisal systems and consciousness
7. The circuit is capable of elaborating distinctly difference subjective feelings (not shown in Figure 13.2).

Panksepp (1998) described a small set of 'hard-wired' emotion systems found in mammalian brains. (We will follow Panksepp's convention of identifying the systems by capitalized labels; the capital letters remind

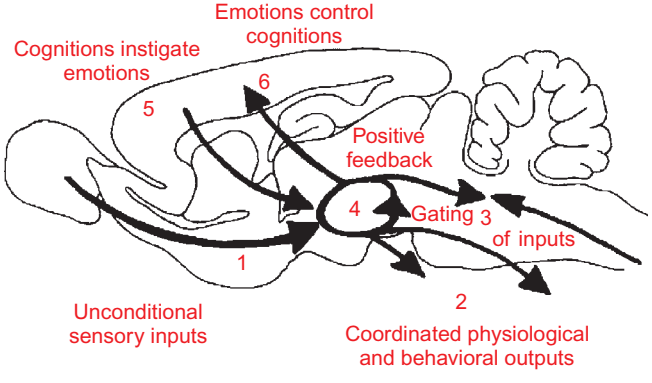


FIGURE 13.2 The functions of emotional systems: (1) unconditioned sensory inputs, (2) coordinated physiological and behavioral outputs, (3) gating of inputs, (4) positive feedback, (5) cognitions instigating emotions, and (6) emotional control over cognitions. *Source*: Panksepp, 2006.

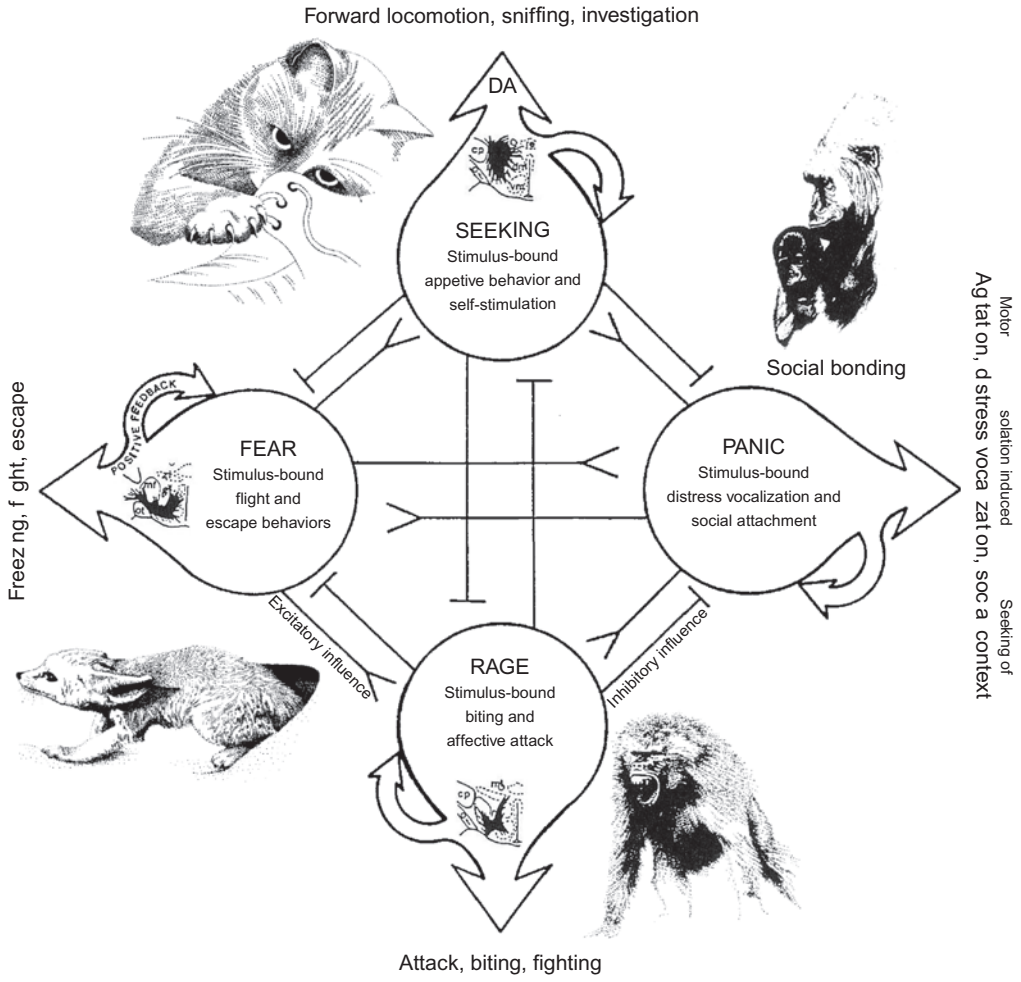


FIGURE 13.3 Four fundamental mammalian emotional systems, shown with prototypical behaviors. *Source*: Panksepp, 1998.

us that we are speaking of systems of emotion and not simply the conscious feelings associated with the systems or single brain locations.) The first four emotion systems appear shortly after birth in all mammals:

- SEEKING: the appetitive system that makes mammals curious about their world and promotes goal-directed behavior toward a variety of goal objects, such as food, shelter, sex
- FEAR: the system which responds to pain and threat of destruction and leads to the well-known flight, fight, or freeze behavior
- RAGE: this system mediates anger and is aroused by frustration, bodily irritation, or restraint of free movement
- PANIC: the system that responds to separation of young animals from their caregiver by activating crying and separation calls.

These four emotional systems and their mutually inhibitory or excitatory relationships with each other are illustrated in Figure 13.3.

In addition to the four fundamental emotion systems, three other special-purpose systems come online at different stages of mammalian development. They are:

- LUST: the system that coordinates sexual behavior and feelings
- CARE: the care giving system that is the adult counterpart of the infant PANIC system; CARE operates in both mothers and fathers and promotes social bonding and care giving behaviors
- PLAY: the neural system that organizes rough-and-tumble play which occurs spontaneously in mammalian young; this system supports laughter and may be the neural substrate of joy.

Since each of these emotional systems has its own 'wiring diagram', understanding emotion in the brain can become quite complex!

Much of what we know about the mammalian emotional systems (shown in Table 13.1) comes from studies of non-human mammals. Studies of emotion

TABLE 13.1 Basic emotional systems in the brain and associated brain areas (adapted from Panksepp, 2006)

Basic emotional system	Associated mammalian brain areas	Associated emotional feelings
FEAR/anxiety	Central and lateral amygdala to medial hypothalamus and dorsal PAG	Fear, anxiety
SEEKING/ expectancy	Mesolimbic outputs of the VTA to the nucleus accumbens; mesocortical VTA outputs to orbitofrontal cortex; lateral hypothalamus to PAG	Interest, curiosity
RAGE/anger	Medial amygdala to bed nucleus of the stria terminalis (BNST); medial and perifornical hypothalamic to PAG	Anger, contempt
PANIC/ separation distress	Anterior cingulate, BNST, and preoptic area; dorsomedial thalamus, PAG	Sadness, shyness, guilt/shame
LUST/sexuality	Corticomedial amygdala, BNST; preoptic area, VTA, PAG	Erotic feeling, jealousy
CARE/ nurturance	Anterior cingulate, BNST; preoptic area, VTA, PAG	Love
PLAY/joy	Dorsomedial hypothalamus; parafascicular area, PAG	Joy, happiness

PAG = periaqueductal gray matter is located in the interior of the midbrain, surrounding the cerebral aqueduct, running from the posterior commissure rostrally to the locus coeruleus caudally. BNTS = bed nucleus of the stria terminalis is a cluster of subcortical nuclei medial to the basal ganglia and above the hypothalamus. VTA = ventral tegmental area which is located in the midbrain.

in human participants are limited by ethical constraints on use of invasive techniques and on the kinds and intensities of emotional stimuli that can be used to evoke emotional responses. Laboratory studies of human emotion rely on behavioral observation and neural imaging following relatively *mild* emotion-evoking tasks such as direct sensory stimulation and conditioning, observation of images of emotional events involving others, and emotion generation through recall and mental imagery of emotion-laden memories. Additional evidence comes from examination of neurological patients who have suffered lesions in various brain areas.

2.1 Feelings of emotion

Feelings of emotion cannot be studied in non-human mammals, though we can make some guesses about the felt experiences of other mammals by observing their behavioral reactions. There is currently considerable debate about whether any evidence justifies speaking of 'feelings' in non-human mammals. It appears that there is growing sentiment in favor of this position based on commonality of neuroanatomy of emotion and of the systems underlying conscious experience.

Damasio *et al*. (2000) studied the neural substrates of emotional feelings in humans. They looked for brain areas active during different emotional states when participants were asked to recall and re-experience emotion-laden personal memories. Using positron emission tomography (PET) imaging, the researchers located significantly different neural maps for fear, happiness, sadness, and anger (Figure 13.4). They noted different patterns of activation and deactivation in cortical and subcortical areas related to the representation and regulation of emotion as well as bodily homeostasis, including insular cortex, secondary somatosensory areas (SII), cingulate cortex, and nuclei in the brainstem and hypothalamus.

Since these emotional experiences were internally generated and did not require either perception of external stimuli or facial or motor expression, Damasio and his colleagues argued that the resulting neural maps represent the neural correlates of the different *feelings* of emotion and conclude:

> The neural patterns depicted in all of these structures constitute multidimensional maps of the organism's internal state, and we believe that they form the basis for an important aspect of mental states known as feelings.

3.0 THE FEAR SYSTEM

We will take a closer look at the FEAR system and the SEEKING system, as described by Panksepp: two emotional systems that have been studied in great detail and that have well-known influences on cognition. Next, we will broaden our focus and look at the fear system in humans and at the reward system, including emotional aspects of rewards: liking, wanting, learning.

The fear system is a neural system for avoiding pain or injury. It is based primarily in the central and lateral nuclei of the amygdala with connections to the medial hypothalamus and dorsal periaqueductal gray matter (PAG) of the midbrain. This system responds to both unconditioned stimuli (loud sounds, looming and sudden movements, painful stimuli, fearful

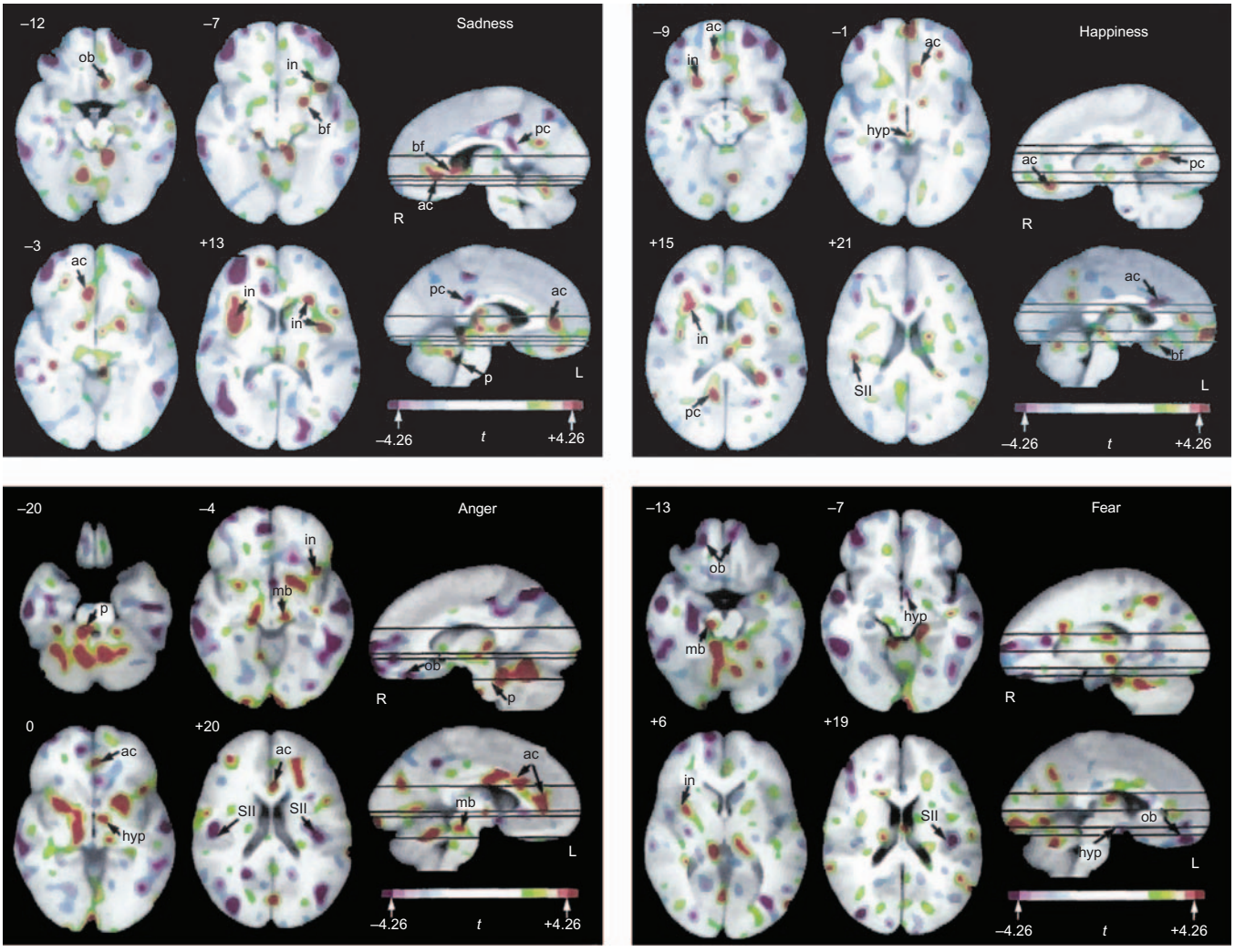


FIGURE 13.4 PET imagery results of participants' self-generated happiness and sadness (top row) and fear and anger (bottom row). Red and yellow indicate areas of increased metabolic activity; purple and blue indicate areas of decreased metabolic activity. Ob = orbitofrontal cortex; in = insula; bf = basal forebrain; ac = anterior cingulate; p = pons; hyp = hypothalamus; pc = posterior cingulate; SII = secondary somatosensory cortex; mb = midbrain. *Source*: Damasio *et al*., 2000.

faces) and conditioned stimuli (classically conditioned danger signals, memories, images) arriving from the thalamus and sensory and association cortices (Figure 13.5). Reciprocal efferent pathways return feedback signals to these thalamic and cortical sites to tune sensory processing in emotion-specific ways (Figure 13.6). It is clear that the efferent (outgoing) pathways *from* the amygdala to cortex are as complex and rich as the afferent (incoming) pathways from cortex *to* the amygdala.

Afferent signals to the amygdala arrive via four pathways. *Olfactory information*, important for mammals, arrives directly at the amygdala from the olfactory cortex without preprocessing in the thalamus; this may account for the profound ability that odors have to evoke emotional memories. *Visceral information* reaches the amygdala from the hypothalamus and septal area through the stria terminalis. *Affect-relevant information about internal states* also arrives from the hypothalamus, thalamus, and brainstem as well as the orbital cortex and anterior cingulate cortex via the ventral pathway. Finally, sensory information arrives directly from *temporal lobe structures* such as the primary auditory cortex and the hippocampus.

The amygdala itself is a collection of nuclei and internal pathways that serve different functions in emotional processes: the *basolateral complex*, the *centromedial nucleus*, and the *cortical nucleus*. The basolateral complex can be further subdivided into lateral, basal, and accessory-basal nuclei. The lateral amygdala, which is afferent to the rest of the basolateral complex as well

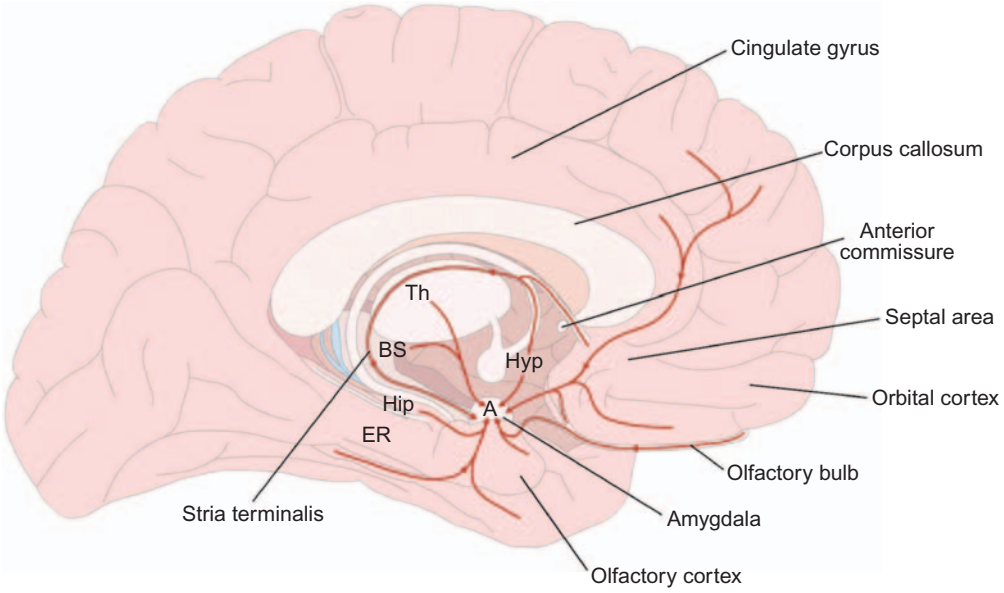


FIGURE 13.5 Afferent pathways to the amygdala. Hip = hippocampus; BS = brainstem; Th = thalamus; Hyp = hypothalamus; A = amygdala.

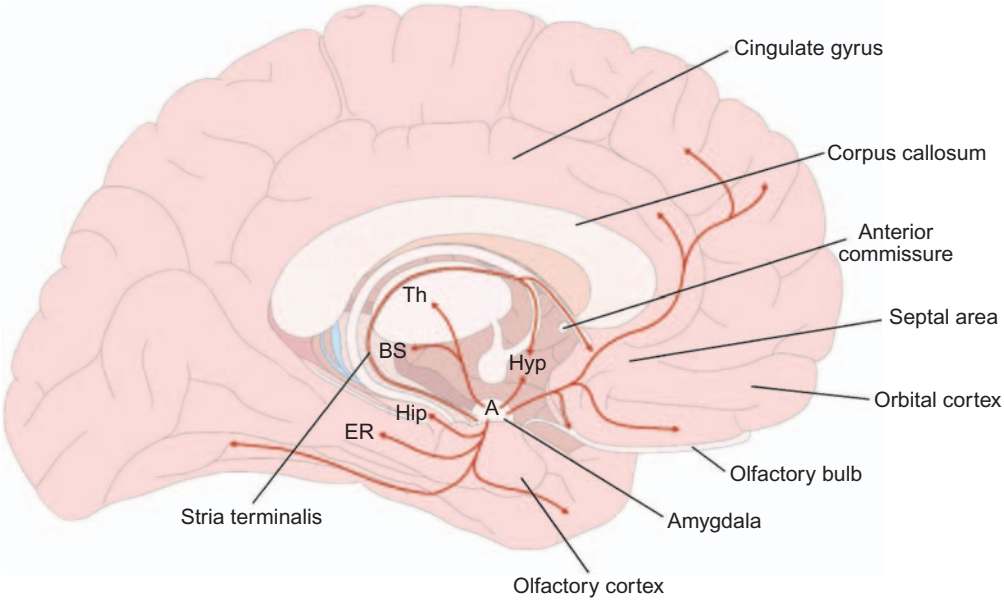


FIGURE 13.6 Efferent pathways from the amygdala. Hip = hippocampus; BS = brainstem; Th = thalamus; Hyp = hypothalamus; Am = amygdala.

as the centromedial nucleus, receives input from sensory systems. The centromedial nucleus is the main output for the basolateral complex, and is involved in emotional arousal in mammals. The cortical nucleus is involved in smell and pheromone processing; it receives input from the olfactory bulb (Figure 13.7).

Efferent pathways from the amygdala mirror afferent pathways, returning signals to subcortical locations and to the brainstem. Of significance for our study of cognition-emotion interactions is the direct efferent pathway from the amygdala to entorhinal cortex, inferior temporal lobe cortex, and finally to visual cortex including the fusiform face area (Figure 13.7). There are *top-down* and *bottom-up relationships* between amygdala and cortex as they work together to tune the brain for adaptive responses to significant environmental threats.

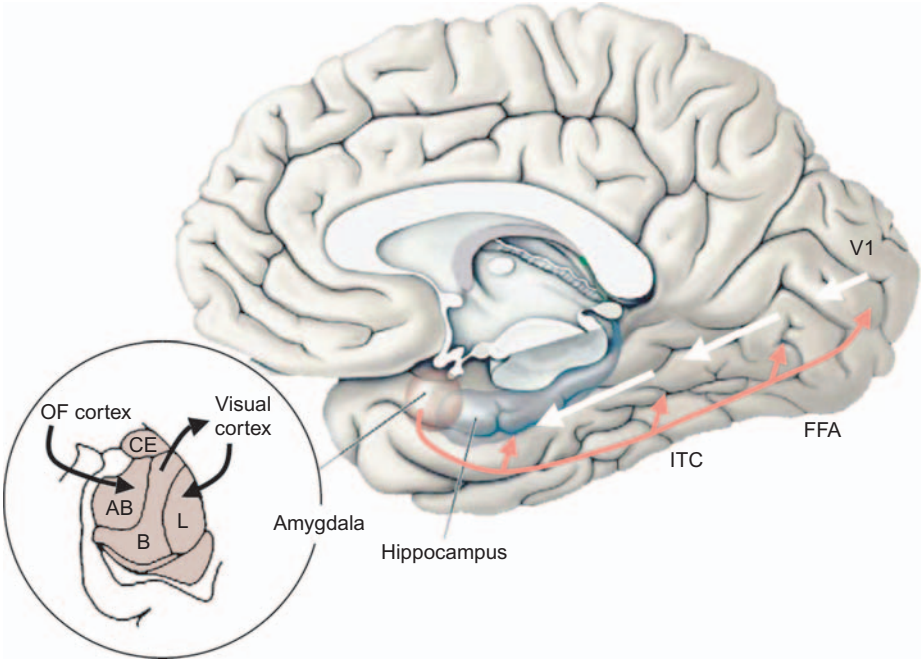


FIGURE 13.7 The nuclei of the amygdala and their efferent connections with sensory cortex. CE = centromedial, L = lateral, B = basal, and AB = accessory-basal nuclei of the amygdala. ITC = inferior temporal cortex; FFA = fusiform face area; V1 = primary visual cortex. Remember that there is an amygdala in each hemisphere of the brain. *Source*: Vuilleumier, 2005.

While most of the research on the neuropsychological function of the amygdala and its functioning has been done on rat and other mammalian models, accumulating evidence from human studies has yielded mostly consistent results. Subcortical emotional systems of the brain are thought to be *conserved* across mammalian groups; the same brain structures operate in the same ways in diverse animals. Most researchers believe that findings from rats and other mammals will apply to human neuropsychology. However, research is ongoing to confirm this hypothesis. Among early human studies confirming the role of the amygdala in fear learning, LaBar *et al*. (1998) found that fear conditioning in humans resulted in an increased blood-oxygen-level-dependent (BOLD) signal in the amygdala as assessed with functional magnetic resonance imaging (fMRI) and that the magnitude of this BOLD response was predictive of the strength of the conditioned response.

3.1 Conscious and unconscious fear processing: LeDoux's high road and low road

LeDoux (1996) labeled the two sensory input pathways to the amygdala for perception of fearful stimuli the 'low road' and the 'high road'. The low road is a fast pathway from sensory receptor to sensory thalamus to the amygdala that bypasses the cerebral cortex (Figure 13.8). As we discussed at the beginning of the chapter, the direct thalamo-amygdala (low road) processing is only capable of low spatial resolution of stimuli and thus can respond only to simple stimuli or to the gross characteristics of complex stimuli. This 'quick and dirty' processing enables automatic, unconscious reactions to the broad outlines of potentially dangerous stimuli before we have to time to think about our responses.

The longer thalamo-cortico-amygdala pathway (high road) takes somewhat longer to traverse but allows complex, contextualized processing of stimuli followed by conscious, deliberate responding. The high road represents the pathway that is more influenced by social and personal decision-making processes and thus can reflect culture-specific emotional responses.

3.2 Fear without awareness

Support for the hypothesis that emotional stimuli can be processed via alternate conscious and non-conscious pathways comes from research from a number of studies. We will look at one conducted by Vuilleumeir and his colleagues (2002). They looked for differential neural responses to fearful and neutral stimuli when processed with and without conscious awareness in a patient with right parietal neglect and visual extinction due to damage in his right inferior parietal cortex (Figure 13.9).

Parietal neglect is a deficit in body perception and visuospatial processing in individuals who have lesions in their parietal cortex. Patients with right

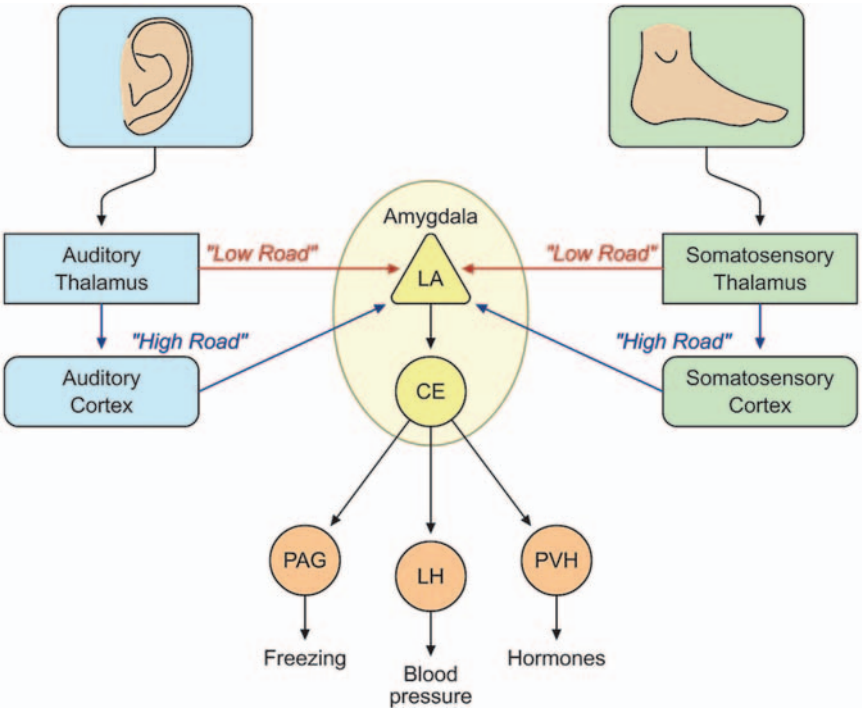


FIGURE 13.8 Two pathways to fear: the low road and the high road.

parietal damage may have difficulty perceiving stimuli shown to them in the part of their visual field contralateral (on the opposite side) to the lesioned area – in the left visual field. In the laboratory, when shown single stimuli in the right or left visual fields, neglect patients have no difficulties with perception. However, when shown two different, simultaneously presented stimuli in the right and left visual fields, patients with right parietal neglect will frequently report not being able to see the stimulus presented to their left visual field. This phenomenon is called *extinction*. It provides researchers with an opportunity to study stimulus processing with and without conscious perception of the stimulus.

Vuilleumeir *et al*. (2002) showed their participant pictures of fearful faces, neutral faces, or a house, individually or together, as shown in Figures 13.10 and 13.11. The important results involved spared processing of faces in the right hemisphere despite parietal damage and the participant's self-reported inability to see the stimuli.

Vuilleumier and his colleagues found that:

1 Fearful faces (but not neutral faces) activated the left amygdala, extrastriate (visual) cortex, bilateral orbitofrontal cortex, and right and left fusiform gyri *when seen and when extinguished*.
2 There was no difference in processing of the fearful faces in the amygdala whether seen or extinguished. Fearful faces can be processed without awareness despite the damaged parietal areas.

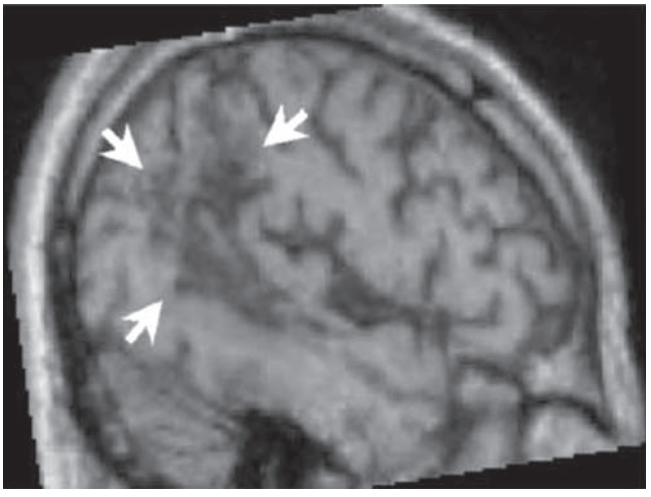


FIGURE 13.9 Damaged right inferior parietal cortex in Vuilleumeir *et al*. (2002) participant. *Source*: Vuilleumeir *et al*., 2002.

3 Conscious perception increased activity in the left fusiform, parietal, and prefrontal cortices of the left hemisphere compared with processing during extinction trials. Consciousness alters cortical processing.

Separate results from non-lesioned participants confirm that *attention to stimuli* (for both task-relevant and non-task-relevant stimuli) and the *emotional significance* of stimuli (fearful or neutral) make independent contributions to visual perception (Vuilleumier *et al*., 2001). Activity in the fusiform gyrus of the ventral

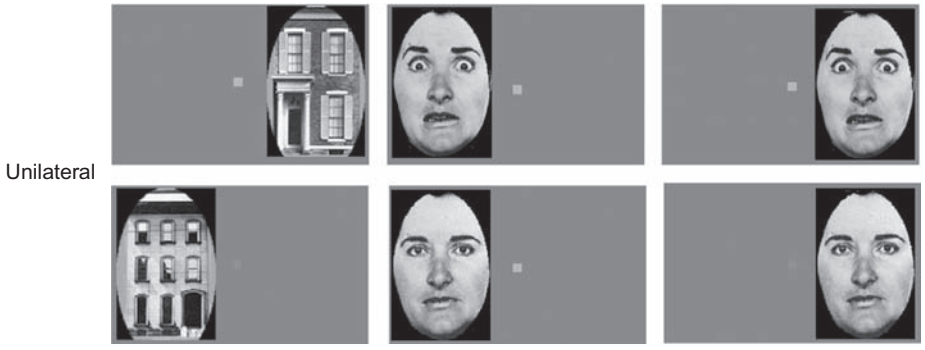


FIGURE 13.10 Unilateral stimuli used by Vuilleumeir *et al*. (2002). When the participant fixated on the light square, the figures projected either to the contralateral right or left hemisphere. He was able to see these figures 100 percent of the time. *Source*: Vuilleumier *et al*., 2002.

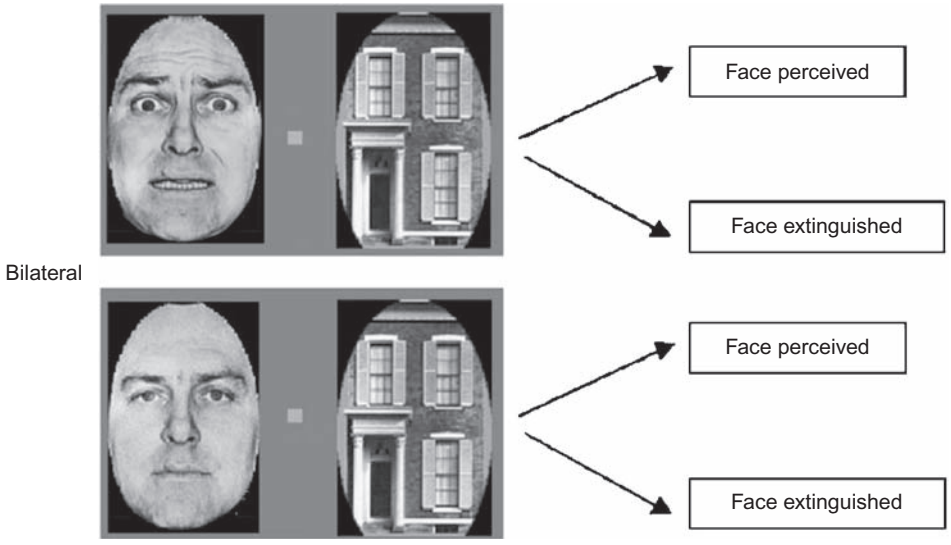


FIGURE 13.11 Bilateral stimuli. When the participant fixated on the light square, he reported being unable to see the faces (projected to his damaged right cortex) about 65 percent of the time. *Source*: Vuilleumier *et al*., 2002.

temporal lobe is greater for attended stimuli than for non-attended stimuli; fusiform activation is greater for fear faces regardless of attentional level (Figure 13.12).

The findings support the idea that there are independent *conscious* and *unconscious pathways* to the fear processing system of the amygdala.

3.3 Affective blindsight

We have known for some time (Weiskrantz, 1986) that patients with lesions in their visual cortex have a preserved ability to respond to the visual features of objects presented in the corresponding blind visual field. Even though such patients have no awareness of the stimuli and cannot describe them, they can, nevertheless, react in behaviorally appropriate ways to specific objects, i.e. they can make appropriate grasping movements with their hands, they can 'guess' at above chance levels the direction of movement, orientation, and color of objects. This ability has been called *blindsight*. Recently, researchers have begun to simulate blindsight in the laboratory by using transcranial magnetic stimulation (TMS) temporarily to interrupt processing in the visual cortex (Ro *et al*., 2004). This research seems to confirm the long-held belief that such non-conscious visual processing depends on sensory abilities of the evolutionarily ancient superior colliculus.

The term *affective blindsight* has been coined to refer to the preserved ability of patients with visual cortical lesions to respond to the *affective qualities* of stimuli shown to them in their blind visual field (de Gelder *et al*., 2000; Heywood and Kentridge, 2000).

de Gelder *et al*. (2005) were able to study the interaction of conscious and unconscious emotional processing in a participant with extensive left visual cortex lesions by presenting facial expressions simultaneously to the intact and blind visual fields. By examining the participant's report of consciously experienced stimuli, the researchers could look for effects of the non-conscious stimuli on conscious reports. When the conscious and non-conscious fear stimuli were congruent (fear seen face with a fear unseen face), correct identification of facial expression was high. However, for incongruent faces (happy seen face paired with fear unseen face or vice versa), the

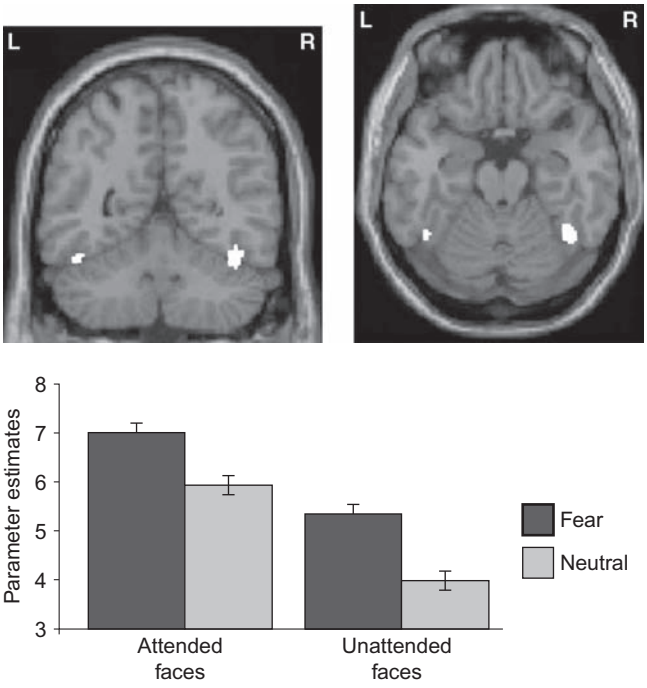


FIGURE 13.12 Activity in the fusiform face area of the temporal lobe: contributions of attention and emotion. *Top left*: Coronal section showing fusiform activity. *Top right*: Horizontal section showing fusiform activity. *Bottom*: Effects of attention and emotion on level of fusiform activation. *Source*: Adapted from Vuilleumier *et al.*, 2001.

correct identification dropped off to chance level. In congruent fear face trials, there was increased activity in the left amygdala, leading researchers to conclude that unconscious processing of unseen fear faces influenced conscious processing and that this effect was mediated by the amygdala and superior colliculus. In an additional experiment, the researchers looked at the influence of seen and unseen faces on perception of an emotional voice (happy or fearful). For congruent fear face and fear voice, perception of the voice was much more accurate than when the face and voice were incongruent – irrespective of whether the face was consciously or non-consciously processed. Unseen happy faces and emotional pictures other than faces did not have similar enhancing effects. Overall, the researchers concluded that recognition of fear is mandatory and independent of awareness. There are separable cortical and subcortical pathways for perception of fearful stimuli.

3.4 Cognition-emotion interactions in fear responses

Now that we understand the basic wiring diagram of the amygdala's inputs and outputs, we can begin to examine cognition-emotion interactions that depend on the amygdala and its associated areas.

A recent review of the role of the amygdala in emotional processing (Phelps and LeDoux, 2005) identified five areas in which there is converging evidence from animal and human studies of cognition-emotion interactions involving the amygdala:

1. implicit emotional learning and memory
2. emotional modulation of memory
3. emotional influences on perception and attention
4. emotion and social behavior
5. emotion inhibition and regulation.

We will look at paradigmatic studies involving human participants.

3.5 Implicit emotional learning and memory

Implicit memory has been discussed in an earlier chapter. It is a kind of learning that is demonstrable in behavioral indicators but that cannot be recollected or consciously reported. It includes various kinds of procedural knowledge, grammars of languages, and classically conditioned associations. Implicit emotional memory involves retention of classically conditioned emotional relationships that cannot be voluntarily recollected or reported. One kind of evidence comes from patients with various kinds of neurological damage.

Patients with damaged amygdalas but spared hippocampi fail to show the physiological indicators of fear conditioning (heart rate increases, electrodermal responses, etc.), but they can recollect and report episodic memories of the circumstances around the fear conditioning. Conversely, patients with lesions in the hippocampus where the amygdalas are spared are unable consciously to report the events surrounding the fear conditionally but show normal fear conditioning measured physiologically (Bechara *et al.*, 1995). This dissociation between the physiological expression of fear conditioning (amygdala-dependent) and the episodic reporting of events surrounding conditioning (hippocampus-dependent) suggest that there are multiple systems supporting emotional memories.

Clinical psychologists who work with victims of traumatic events (accidents, abuse, combat) also have an interest in implicit emotional memory.

3.6 Emotional modulation of explicit memory

Psychological evidence has been available for some time indicating that moderate levels of emotional

arousal (most often fear-based arousal) at the time of an event lead to better retention of explicit memories. For example, frightening films are better remembered than neutral films, with a linear relationship between degree of emotional arousal in the film (measured by self-report and by PET activity in the amygdala) and level of free recall (Cahill *et al*., 1996). The familiar inverted U-shaped function is in operation in predicting the interaction of emotion and memory consolidation. Too much activation in the amygdala leads to loss of explicit memories for emotional events (Cahill and McGaugh, 1998).

Pathways to consolidation of explicit memories seem to depend on reception of emotional stimuli by the amygdala, followed by activation of the hypothalamus and pituitary gland, resulting in release of the adrenomedullary hormone adrenaline and subsequently the adrenocortical hormone cortisol. Both adrenaline and cortisol (often called stress hormones) appear to influence the hippocampus-dependent formation of explicit memories (Figure 13.13). Improved memory for emotional stimuli is absent in patients with bilateral amygdala lesions (Cahill *et al*., 1995). The arousal effect due to stress hormone release can also be eliminated by administering β-adrenergic antagonists ('beta blockers' such as propanolol) that block adrenaline receptors (Cahill *et al*., 1994). The hyper-responsivity of post-traumatic stress disorder (PTSD) patients can be ameliorated by administration of propanolol in the emergency room soon after traumatic events (Pitman *et al*., 2002).

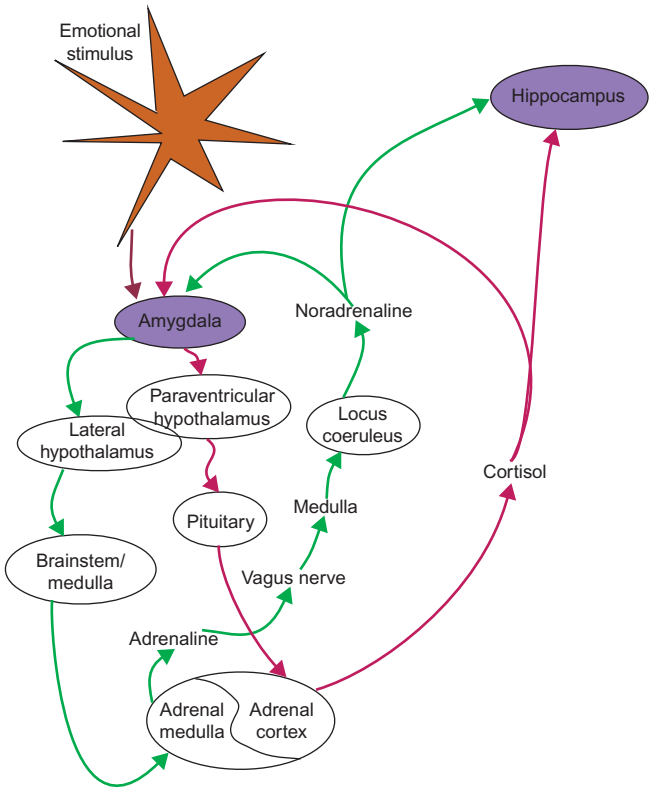


FIGURE 13.13 Stress hormones and explicit memory consolidation. Adrenaline pathway: green. Cortisol pathway: red. Notice that both pathways begin in the amygdala, circulate to the adrenal gland, and feed back to the amygdala and hippocampus after passing throughout the body.

3.7 Emotional influences on perception and attention

One of the defining features of emotional systems, according to Panksepp's criteria (presented at the beginning of the chapter), is that emotional circuits can influence higher level processing. Evidence for such influence has been obtained in non-human mammals where fear conditioning was found to alter the neural representation of the conditioned stimulus (CS) in the auditory cortex. Studying the guinea pig, Bakin *et al*. (1996) found that classical conditioning of tones shifts the tuning frequency of individual cortical neurons toward the frequency of the CS. The researchers report that such receptive field plasticity is associative, highly specific, rapidly acquired, and indefinitely retained.

Parallel but more limited findings have been obtained for human participants. As we have seen above, the amygdala has direct and indirect connections to sensory cortices that are possible pathways for positive feedback to perceptual processes. Imaging studies using visual masking methods and subliminal fear conditioning (Morris *et al*., 2001) have shown that human participants who are subliminally exposed to face stimuli as CS for an aversive loud noise (UCS) show an increased responsiveness in the amygdala and visual cortex over trials to the CS. The researchers concluded that 'the parallel learning-related responses observed in ventral amygdala and visual cortex are consistent with a proposal, therefore, that "feedback" efferents from basal amygdala nuclei mediate emotion-dependent modulation of visual processing'.

The amygdala appears to play a role in determining how unattended but significant stimuli gain access to consciousness by temporary feedback to cortical areas involved in receiving sensory input. The action of the amygdala can make the cortical areas momentarily more receptive to certain adaptively important stimuli.

An example of this greater receptivity to significant stimuli can be found in the Stroop test (Box 13.1) when personally emotion-evoking words are compared with

BOX 13.1 Emotional Stroop test

A version of the emotional Stroop test that influenced responding by Vietnam veterans (adapted from McNally *et al.*, 1990)

Controls	War-related	Negative	Neutral	Positive
OOOOOOO	firefight	germs	mix	loyal
OOOOOOO	Medevac	filth	millionaire	pleasant
OOOOOOO	Nam	dirty	concrete	happy
OOOOOOO	bodybag	urine	input	friendship

other positive, negative, and neutral words. The result has been obtained with Vietnam veterans (McNally *et al.*, 1990) as well as civilian trauma survivors (Taylor *et al.*, 2006). Words that have personal significance for participants (body bags, 'Nam, Medevac for the Vietnam veterans versus revolver, incest, 9/11, or fire for civilian victims) are repeatedly found to gain access to awareness more readily than neutral words and, consequently, cause greater delay in naming the color of the ink in which the words are printed. However, patients who have suffered bilateral damage to the amygdala fail to show the expected facilitation of attention for emotional words than is found in normal participants. Though participants with amygdala lesions comprehend the meaning of the words, they do not display selectively enhanced perception of verbal stimuli with aversive content (Anderson and Phelps, 2001).

3.8 Emotion and social behavior

Bilateral damage to the amygdala in monkeys causes dramatic changes in their behavior, including lack of fear for dangerous stimuli, eating inedible objects, and atypical sexual behavior (Kluver-Bucy syndrome). However, parallel behavioral changes have not been noted in human patients with lesions of the amygdala, presumably because humans have extensive neocortical social control and inhibition systems not available to other primates. There is, however, some evidence that more subtle deficits exist in patients with amygdala damage, for example, in processing of emotional facial expressions.

As we noted at the beginning of the chapter, the amygdala responds to simple aspects of complex stimuli, specifically to low spatial frequency aspects of faces (Vuilleumeir *et al.*, 2003). Consistent with this general rule, evidence shows that the amygdala responds to the wide-open eyes of fearful and surprised expressions. In a recent refinement, Whalen and his colleagues (Whalen *et al.*, 2004) found that the amygdala responded selectively to subliminally presented *whites* of fearful eyes compared to the whites of happy eyes (Figure 13.14).

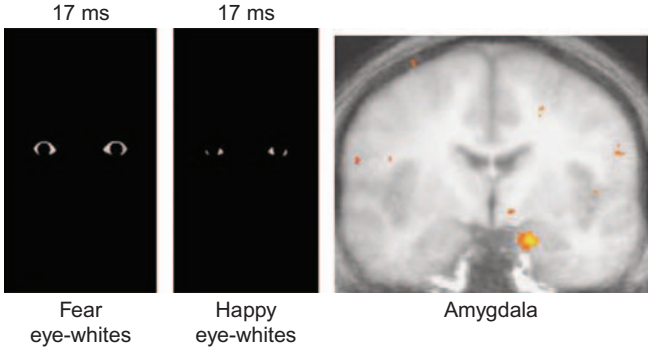


FIGURE 13.14 Amygdala responds to the whites of fearful eyes more strongly than to happy eyes. On the right, the BOLD response of the left ventral amygdala to fearful whites. *Source*: Whalen *et al.*, 2004, as adapted in Phelps and LeDoux, 2005.

Finally, Adolphs *et al.* (2005) found that patients with bilateral amygdala damage fail to look at the eyes when judging facial expression. This deficit may account for observed difficulties in interpretation of others' emotion among such patients. Patients with amygdala lesions underestimate emotional intensity and overestimate trustworthiness and approachableness of others compared to non-lesioned participants.

3.9 Emotion inhibition and regulation

Fear learning is a long-lasting and stable kind of learning that is remarkably resistant to change and voluntary control. It is very difficult to think one's self out of a fearful response. While fear learning is adaptive in that it allows us to avoid predictable dangers in the environment, it can become disabling if it is misplaced or exaggerated. Research on modification or elimination of emotional associations by extinction or reversal, reconsolidation, and emotion regulation is of considerable importance.

Extinction is a method of Pavlovian conditioning where a conditioned stimulus (CS) that was previously linked to an aversive unconditioned stimulus (UCS) is presented alone for a number of trials. The participant learns that the CS is no longer a signal for the aversive event in that context. The CS will continue to evoke the fear response after the passage of time, in other locations, with re-exposure to the UCS. This shows that the learned fear response has been retained in memory and that extinction learning operates by inhibiting the fear response.

The neuroscience of extinction is well studied. It depends critically on the activity of NMDA receptors in the amygdala. When NMDA receptors are blocked in rats, extinction learning is disrupted. When activity at NMDA receptors is enhanced, extinction is augmented. Recently, researchers (Ressler *et al*., 2004) used NMDA agonists for the first time to improve extinction learning in human agoraphobic patients. They found that two doses of D-cycloserine significantly reduced agoraphobia in conjunction with exposure therapy compared to therapy with a placebo, assessed by self-report and by electrodermal responses to the UCS. The improvements were maintained at three months post-treatment. These results suggest possibilities for future treatments of negative emotion that rely on the neuroscience of fear in the amygdala.

Reversal conditioning is similar to extinction learning in that it modifies the contingencies between conditioned stimuli and responses. In this paradigm, participants are first conditioned to fear one stimulus (CS+) which is reliably followed by a fear-inducing stimulus (UCS), such as a loud noise, and not to fear another stimulus (CS−) which is never followed by the UCS. In the next phase, the contingencies are reversed so that the previously neutral stimulus is now paired with the UCS.

Morris and Dolan (2004) used reversal conditioning to explore the role of the amygdala and the orbitofrontal cortex in fear conditioning. They used a neutral facial expression as CS+ with a loud noise as UCS. They found that during initial conditioning, strong bilateral activation in the amygdala developed to the CS+. After reversal, the new face CS elicited enhanced responses in the orbitofrontal cortex while the old CS continued to evoke increased responses in the right ventral amygdala. While the orbitofrontal cortex is capable of rapid reversal of fear responses, the amygdala showed a persistent, non-reversing response to previous fear-related stimuli. Cortex and limbic system seem to follow different programs – cortex is rapidly responsive to new contingencies while limbic system is more conservative and retains old triggers.

This finding speaks to the neurological basis of the experience of 'being of a divided mind' where part of us knows that the danger no longer exists and part of us still responds to old cues. Those who live with post-traumatic stress disorder (PTSD) are quite familiar with this non-voluntary kind of responding despite changed circumstances.

Memories, including fear memories, become permanent through a process of protein synthesis called consolidation. When retrieved, the memory again becomes labile and is susceptible to further manipulation and alteration prior to *reconsolidation*. Evidence shows that reconsolidation of fear memories in rats involves additional protein synthesis in the amygdala (Nader *et al*., 2000). Infusion of an antibiotic that interrupts protein synthesis eliminates the conditioned response at test the next day. To date, no direct studies of protein synthesis and reconsolidation involving human participants have been published. It is a promising line of future research with the potential to alleviate PSTD symptoms.

Finally, emotional responsiveness can be regulated to some extent by top-down influences from cortex to amygdala. *Reappraisal and reinterpretation* of events are primary coping strategies for human beings. We can reappraise circumstances and attempt to see them in a different way with different meanings and implications for us. For example, we can reinterpret taking a wrong turn from an inconvenience and time-waster to an opportunity to explore new territory. We thereby change our emotion from frustration to curiosity. Reappraisal can lead to both down-regulation as well as up-regulation of affect. Such reappraisal alters our subjective experience as well as our physiological responses. In general, reappraisal strategies activate prefrontal and anterior cingulate cortex involved in cognitive control and the amygdala increasing or increasing activation in parallel with emotional arousal.

Ochsner and his colleagues (Ochsner *et al*., 2004) looked for fMRI correlates of reappraisal of pictured negative events. They looked for areas of brain activation when participants up-regulated or down-regulated

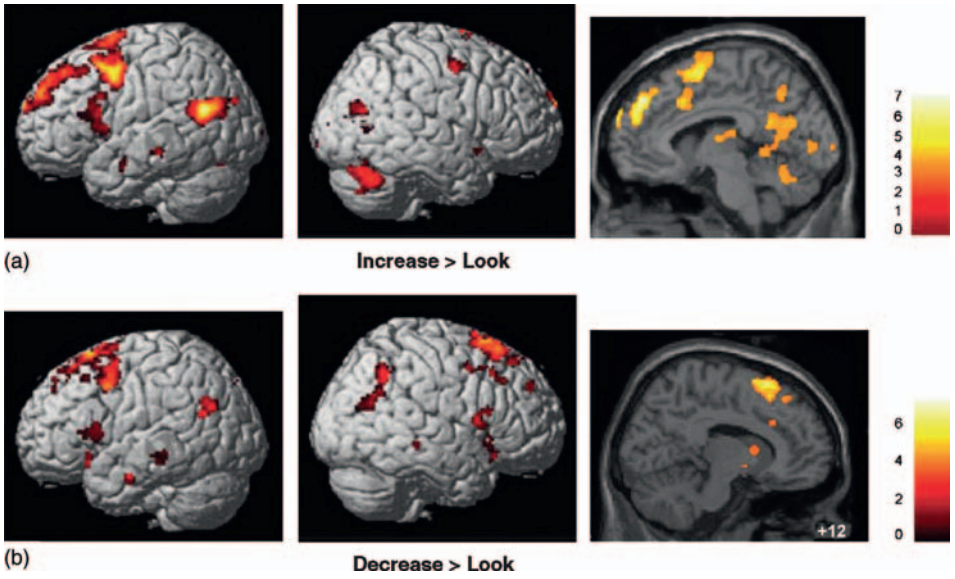


FIGURE 13.15 Up and down regulation. Activations for appraisal strategies compared to looking at pictures without appraisal. (a) Activation related to up-regulation of negative affect. Lateral views are shown on the left and center; medial views on right. Note left dorsal lateral and medial prefrontal as well as anterior cingulate cortical activation. (b) Views for down-regulation. Note bilateral activation of lateral and medial prefrontal cortex, including many left-sided regions similar to those used when increasing affect. *Source*: Ochsner *et al.*, 2004.

negative affect related to pictured negative events, such as a sick person in the hospital. Participants were assigned one of two kinds of appraisal strategies. In the *self-focus group*, they were asked to focus internally on the meaning of the negative event – either *up-regulating* the negative affect by imagining themselves or someone they love as the person in the picture or *down-regulating* by increasing personal distance from the event by seeing it from a detached objective perspective. In the *situational focus group*, participants were asked to consider aspects of the situation either imagining that things would get better (down-regulating negative affect) or imagining that things would get worse (up-regulating negative affect).

Both up- and down-regulating negative emotion recruited prefrontal and anterior cingulate regions commonly implicated in cognitive control. Amygdala activation was modulated up or down in accord with appraisal strategies used. Up-regulation uniquely recruited regions of left rostromedial PFC implicated in the retrieval of emotion knowledge, whereas down-regulation uniquely recruited regions of right lateral and orbital PFC implicated in behavioral inhibition (Figure 13.15).

Results also indicated that self-focused regulation recruited medial prefrontal regions (BA 32) implicated in internally processing and self-referential judgments. Situation-focused regulation recruited lateral prefrontal regions (BA 46) implicated in maintenance and manipulation of information about the external world via working memory (Figure 13.16).

These data suggest that both common and distinct neural systems support various forms of reappraisal. Particular prefrontal systems modulate the amygdala in different ways depending on the regulatory goal and strategy employed.

We can see that the fear system that gives rise to negative emotion has numerous interactions with cognitive systems in the cortex. We turn now to the system that Panksepp called the SEEKING system, another highly studied emotional system in the brain. In human studies, these aspects of emotional processing are typically referred to as reward systems or pathways, and correspond to human emotions of liking and wanting. We will look at a few examples of cognition-emotion interactions involving the reward system.

4.0 THE REWARD SYSTEM: LIKING, WANTING, LEARNING

To review, Panksepp (1998) described the SEEKING system as the appetitive system that makes mammals curious about their world and promotes goal-directed behavior toward a variety of goal objects, such as food, shelter, sex. This concept of the SEEKING system includes classical *reward pathways* in the brainstem as well as other subcortical areas. In contrast with the FEAR system which gives rise to freezing, hiding, or flight in service of self-protection when activated, the SEEKING system is a positively valenced, energizing system that moves animals out into their environment to forage and explore.

In 1954, Olds and Milner discovered that rats would learn to work for electrical stimulation of the subcortical areas including areas around the lateral

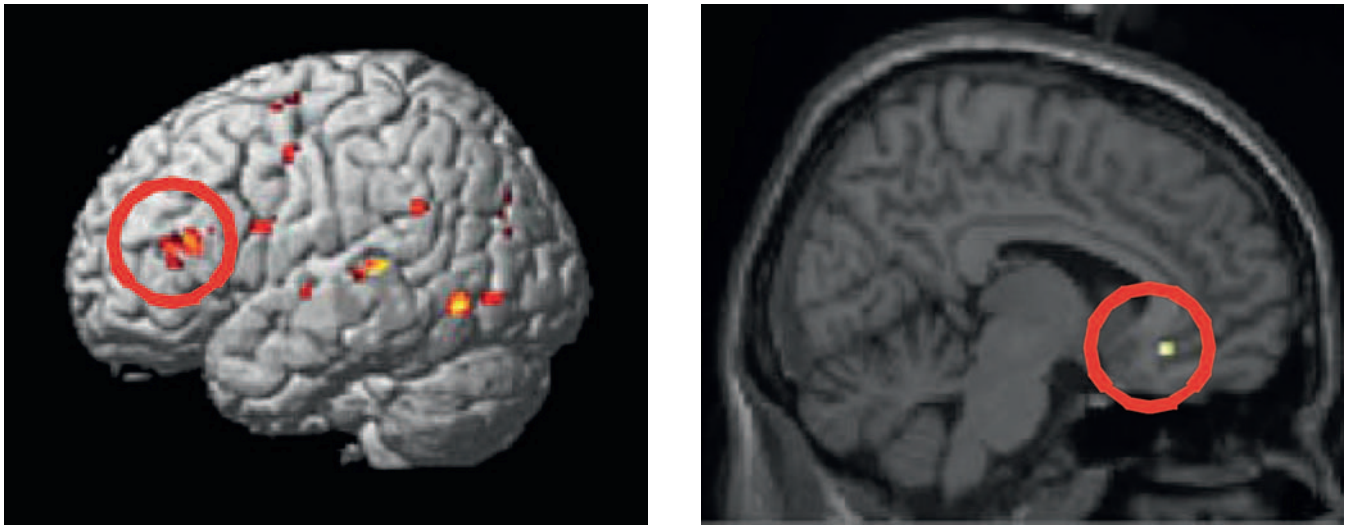


FIGURE 13.16 Situation-focused regulation. Activations unique to appraisal strategies when down-regulating affect. Situation focus on left: notice activity in BA 46 (circled). Self-focus on right: note activity in BA32 (circled). *Source*: Ochsner *et al.*, 2004.

hypothalamus. Subsequent studies have shown this electrical self-stimulation (ESS) is highly reinforcing. Rats will self-stimulate areas in the lateral hypothalamus up to 2000 times an hour and choose ESS over food to the point of starvation. Development of microelectrodes in the 1970s allowed increasingly fine-grained studies of brain locations involved in reward.

The primary reward pathways in mammals include the:

1. mesolimbic dopamine pathway: dopaminergic neurons that originate in the ventral tegmental area (VTA) of the brainstem terminate at the nucleus accumbens in the forebrain and
2. mesocortical dopamine pathway: dopaminergic neurons project from VTA to orbitofrontal cortex (Figure 13.17). VTA is located inside the pons in the midbrain, surrounded by other midbrain nuclei and pathways. Nucleus accumbens is located near and anterior to the amygdala and below the striatum (basal ganglia) in each hemisphere.

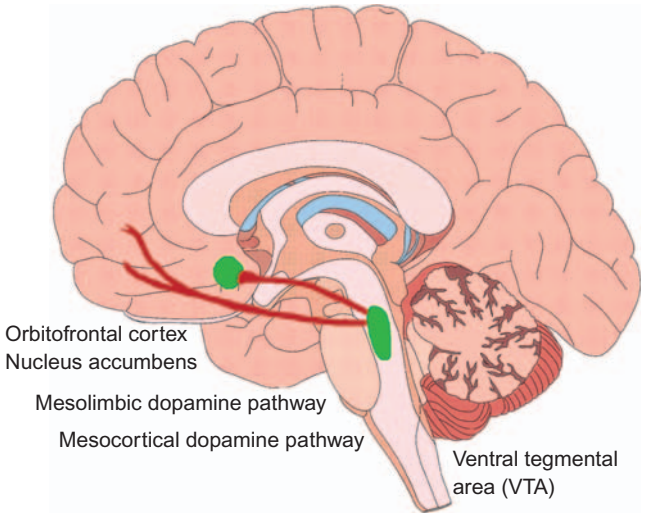


FIGURE 13.17 Dopamine reward pathways including the mesocortical dopamine and mesolimbic dopamine pathways.

4.1 Re-interpreting 'reward': from reward to reward prediction to reward prediction error

Understanding of the reward concept and the role of midbrain dopamine pathways has evolved. For a long time, the dopamine system was thought to respond at *receipt* of rewarding stimuli, such as ESS, intracranial drug injections, food, or sweet water or to conditioned stimuli that predicted the reward. Subsequent research has shown that neurons in this system are more responsive to *anticipation of reward* than to receipt of reward (Schultz, 1998, 2002). Evidence in support of this hypothesis shows that dopamine neurons:

1. fire selectively in response to unexpected rewards and novel, attention-grabbing events, followed by a rapid decrease in responding with repeated arrival of reward as expected
2. stop responding to predictable rewards, as they gradually become responsive to conditioned stimuli that *predict* rewarding events
3. are inhibited by the omission of expected rewards.

The reward system begins with unconditioned responses to sensory aspects of rewarding objects: unconditioned stimuli (UCS) such as sweet tastes, musky smells, etc. Since the primary reinforcing event is actually the arrival of dopamine at the nucleus accumbens, the UCSs are not the rewards. They are proximal cues of upcoming internal events. With experience, more distal, environmental signals such as landmarks and sounds (conditioned stimuli, CS) come to predict the availability of taste and smell-carrying objects. Now these new cues come to evoke dopaminergic responses in the midbrain. Over time, it is the acquired reward stimuli that seem to produce the greatest pleasure. In our own lives, we are more excited about the prospect of a pay raise or a hot date than we are at 'receipt' of these desired events (Wise, 2002). Sadly, at least from the point of view of the dopamine system, there seems to be something to the idea that the desired object, once attained, is no longer as desirable.

The simple reward prediction view has been revised in light of evidence suggesting that dopaminergic neurons respond specifically to *errors in prediction of rewards*. For example, over time, activation disappears to CSs that reliably predict reward. The loss of response is not due to a generalized loss of response to the reward itself, since the dopaminergic system responds to the rewards outside the test situation. Also, response of dopaminergic neurons is depressed when rewards are withheld or delayed when CSs indicate that they should arrive. Since there are no other novel stimuli present at the time when rewards are expected, the depressed response cannot be interpreted as a response to another stimulus. The depressed dopaminergic response when rewards are withheld is seen as a reaction to the failed arrival of a predicted event.

The evidence suggests that dopamine neurons shift responsiveness toward situations where rewards are highly unpredictable. In fact, CSs cannot be conditioned to rewards that are already reliably predicted. The long-standing empirical test for this hypothesis is the blocking paradigm. In the blocking paradigm, it can be demonstrated that a new stimulus will not become associated with a reinforcer when it is presented in a circumstance where the reinforcer is already predicted 100 percent of the time. Direct empirical evidence that the dopaminergic system is involved in mediating this behavioral learning has been obtained in monkeys where microelectrodes record responses of individual dopaminergic neurons.

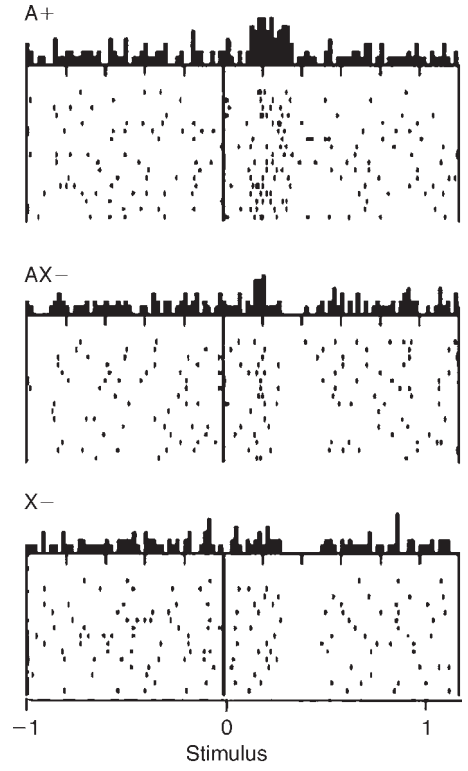


FIGURE 13.18 An example of an individual dopamine neuron that is inhibited by a stimulus predicting reward omission. At the top of each panel is a cumulative histogram of action potential number across time (each bar is 10 ms) for repeated presentations of the stimuli; below each histogram, the dashes represent individual action potentials occurring in each trial. Stimulus 'A' is paired with reward (A+) and excites the dopamine neuron. When 'A' is presented with 'X' no reward occurs (AX−), and therefore 'X' predicts reward omission. When 'X' is presented alone, the dopamine neuron is inhibited (X−). Other control stimuli were also presented but are not shown here. *Source:* Ungless, 2004; this figure was reproduced from Tobler *et al.*, 2003, with permission.

A study by Tobler *et al*. (2003), reviewed by Ungless (2004), showed that dopamine neurons are not activated by all salient stimuli. They trained monkeys by rewarding them every time a light was turned on. Then the light came on, a tone was simultaneously sounded and no reward was delivered (see Figure 13.18); thus the tone predicted the omission of a reward. When the tone was presented alone, the dopamine neuron was inhibited. Ungless (2004) suggested that these findings indicate that dopamine neurons are not activated in a non-specific manner when salient stimuli are presented: it is the stimuli's predictive powers and not just the presence of a reward that modulate dopamine neuron activity.

Currently, reward prediction error theory is the most widely accepted understanding of the dopaminergic reward system.

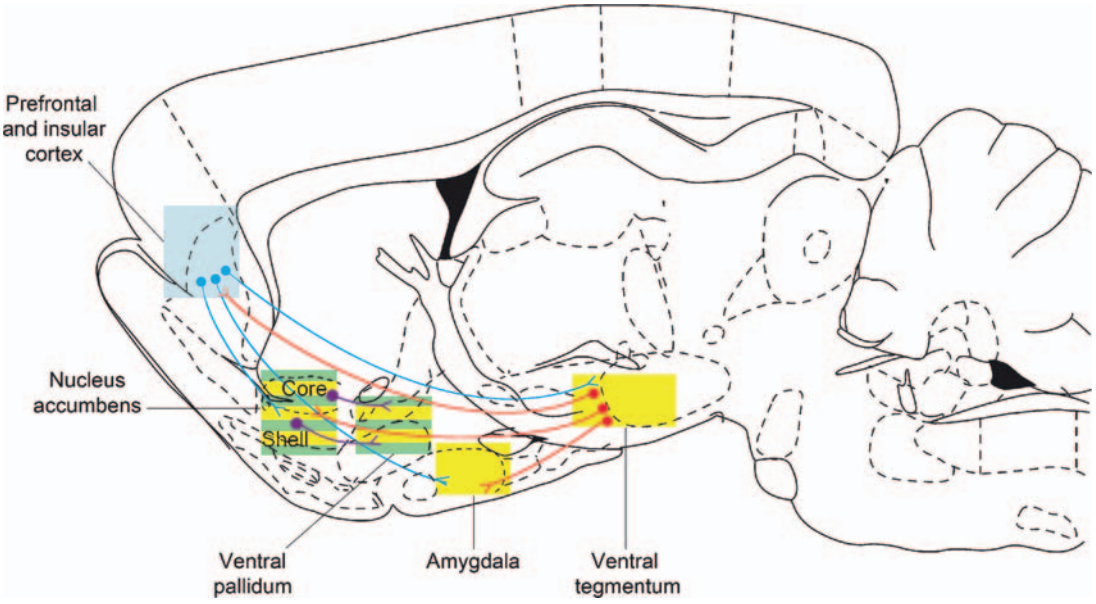


FIGURE 13.19 Simplified view of subcortical liking and wanting pathways, shown in a rat brain. 'Liking' pathways are shown in green; 'wanting' pathways in yellow; cognitive processing of cues is shown in blue. *Source*: Berridge and Robinson, 2003.

4.2 Reward is more than learning

The reward prediction error theory of reward focuses heavily on the learned aspects of rewards. Quoting Thorndike's early view, Schultz (2002) emphasized the function of rewarding events in 'stamping in' associations between conditioned stimuli and their consequences. In response, it has been noted by other researchers (Berridge and Robinson, 1998, 2003; Panksepp, 2005) that reward prediction theory leaves out important hedonic and motivational components of rewarding events that should not be ignored.

The hedonic feeling of 'liking' has been shown to have reliable facial characteristics across different mammals and to be dissociable from the dopamine system. 'Liking' reactions are neurally modulated by a distributed brain network that includes the *shell of the nucleus accumbens*, *ventral pallidum*, and *brainstem parabrachial nucleus* (Berridge and Robinson, 2003; Figure 13.19). Liking reactions to sweet water in rats are not affected by activation or suppression of the mesolimbic dopamine systems but are increased by injections of opioid- or GABA-agonist microinjections. Lesions that eliminate dopamine in the nucleus accumbens and produce a profound aphagia (disinclination to eat) fail to disrupt taste 'liking' (Wyvell and Berridge, 2000). Dopamine receptor antagonists often fail to suppress subjective pleasure ratings of amphetamines and cigarettes in humans. Finally, activation of the human dopamine system by amphetamine correlates better with subjective ratings of wanting for drug or food than with subjective ratings of pleasure (Leyton *et al*., 2002). In subjective terms, the dopamine system makes food and drugs more desired and sought out but does not make them palatable, tasty, or enjoyable once acquired. Likeability apparently depends on a separate system involving the shell of the nucleus accumbens.

It makes some sense in light of this evidence to separate the *learning* aspects of reward, i.e. the ability of rewarded behaviors to be retained, from the hedonic *liking* aspects. Homologies in behavioral responses to tastes give us indicators of the hedonic impact of stimuli (Berridge, 2000). Homologous indicators of 'liking' across species of mammals include tongue protrusion for tastes such as sweet water. Conversely, disliking reactions include open-mouthed gapes to bitter tastes like quinine (Figure 13.20).

A third component of the reward architecture is the element of *wanting* or incentive salience (Berridge and Robinson, 1998). Wanting is separable from liking and learning subjectively and neurologically (Figure 13.21). We can want things, such as drugs of abuse or cigarettes, even when we don't like them. Learning may be motivated by wanting but can take place without wanting. Likewise, learning can take place without subjective 'liking' as when receiving intracranial drug injections for learning lever-pressing responses without

an accompanying sensory experience of a reinforcer. Wanting 'transforms mere sensory information about rewards and their cues (sights, sounds, and smells) into attractive, desired, and riveting incentives' (Berridge & Robinson, 2003 p. 510). In contrast to the liking component of reward, wanting, or in humans, craving is highly dependent on the mesolimbic dopamine pathway.

FIGURE 13.20 Liking reactions: objective indices of hedonic aspects of emotion. Homologous affective facial expressions by infant human, juvenile orangutan, and adult rat to 'liked' sucrose (top) versus 'disliked' quinine (bottom). *Source*: Berridge and Robinson, 2003.

4.3 'Reward pathway' and drug use

All drugs of abuse have their effects on the 'wanting' system via the dopamine pathways and their connections in the midbrain (Figure 13.22). Animals will learn to press a lever to receive intracranial microinjections and acquire conditioned place preferences for locations where they receive such microinjection of drugs. The behavior of these animals has helped to isolate brain areas involved in the rewarding effects of cocaine, amphetamine, nicotine, alcohol, and opiates (Spanagel and Weiss, 1999; Ikemoto and Wise, 2004). In addition, drug effects in humans have been studied by investigating the effect of drug agonists and antagonists on the experience of drugs of abuse by drug-using individuals.

Natural rewards and drugs of abuse act in different ways on the mesolimbic dopamine system. Food, as well as opioids, indirectly affects the reward system by decreasing the action of inhibitory interneurons that normally inhibit the dopaminergic neurons of the

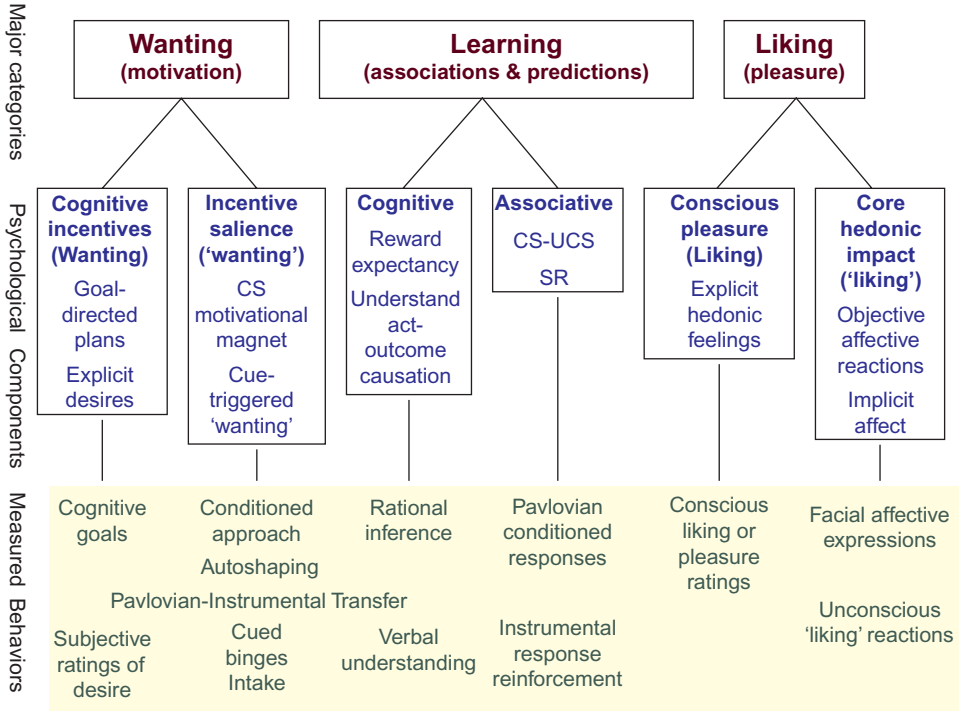


FIGURE 13.21 A schematic of psychological components of Wanting, Learning, and Liking and the measurable behaviors used to investigate them. *Source*: Berridge, 2009.

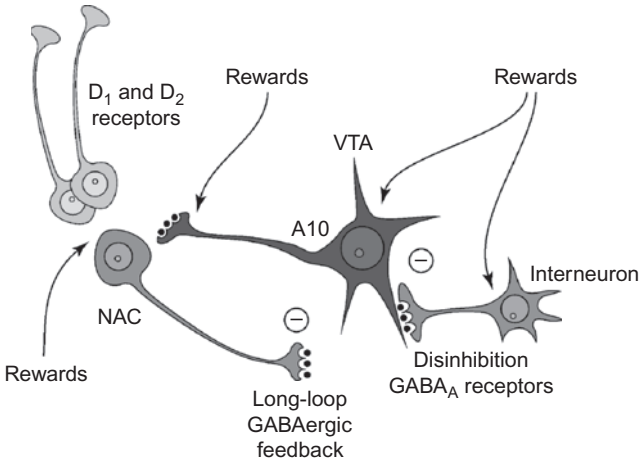


FIGURE 13.22 Drugs and their effects on the 'wanting' system. Direct and indirect activation of VTA dopaminergic activity by natural rewards and drugs in the mesolimbic dopamine system. A10 dopaminergic neurons originate in the VTA and project to the shell of the nucleus accumbens (NAC). GABA-ergic interneurons within the VTA and long-loop GABA-ergic feedback from the NAC provide inhibitory control (minus signs) of the A10 neurons. Different dopamine receptors in the NAC (D_1 and D_2) mediate reward effects. *Source*: Spanagel and Weiss, 1999.

TABLE 13.2 Agents and their effects on behavior: sites implicated in the rewarding effects of natural rewards and drugs of abuse

Agent	Effective site
Food, liquids, sex	Cause dopamine release in VTA through inhibition of GABA-ergic interneurons that normally inhibit the dopaminergic neurons
Mu and delta opioids	Opioids act indirectly through inhibition of GABA-ergic neurons in VTA and NAC that normally inhibit the dopaminergic neurons
Amphetamine	Acts directly to release dopamine in the nucleus accumbens
Cocaine	Acts directly to block the dopamine transporter system/reuptake in the shell of the nucleus accumbens
Phencyclidine (PCP)	Acts directly in the shell of the nucleus accumbens through blockade of NMDA receptors
Cannabis	Acts in the posterior VTA and shell of the nucleus accumbens
Ethanol	Acts indirectly through posterior VTA through inhibition of the GABA-ergic interneurons
Nicotine	Nucleus accumbens/ventral striatum

VTA; the result is increased activity in the dopaminergic neurons of the VTA. In contrast, cocaine and amphetamine act directly in the nucleus accumbens to maintain high levels of dopamine at synapses of dopaminergic neurons; cocaine inhibits reuptake while amphetamine apparently increases dopamine release. The specific modes of action of various drugs are still being investigated. However, it is clear that the agents outlined in Table 13.2 affect behavior and subjective experience through their effects on the mesolimbic dopamine system (Spanagel and Weiss, 1999; Ikemoto and Wise, 2004).

4.4 Reward cues influence attention

Consistent with the reward prediction error view, cues that predict availability of drugs of abuse quickly become conditioned stimuli and powerful evokers of craving in humans. Drug-related cues not only activate the dopaminergic system and create the subjective experience of craving but they also influence cognitive activities. Use of drugs shifts attention toward drug-related cues at the expense of other stimuli. Numerous studies using the Stroop paradigm (discussed earlier) have shown that drug-related cues (pictures and words) divert attention from the color-naming task in drug-using participants but not in non-using participants (Hester *et al*., 2006). Corresponding brain imaging studies have shown that smokers have significantly greater responses to smoking-related picture cues in the nucleus accumbens and neighboring ventral striatum than non-smokers (David *et al*., 2005), though there is no difference between the groups' imaging responses to neutral images.

5.0 SUMMARY

Mammals have separate emotional systems in the brain, each with patterned, innate responses to stimuli in the expected environment of the species related to survival. Systems such as the fear system and the reward system have been shown to have both unconditioned and conditioned responses to significant 'calling conditions' supported by separate neural networks: fear relying on the amygdala and its connections, and the reward system relying heavily on the mesolimbic and mesocortical pathways of the VTA. Each of these systems can come under cognitive control and also reciprocally influence higher decision making, appraisal systems, and consciousness. Each system is capable of elaborating distinctly different subjective feelings.

6.0 CHAPTER REVIEW

6.1 Study questions

1 What are the key differences between the reptilian and the mammalian brain?
2 What are examples of 'hard-wired' emotions as described by Panksepp?
3 Why has the fear system been more studied than other emotion systems?
4 What do the terms 'high road' and 'low road' refer to in terms of fear processing?
5 In what ways has the study of affective blindsight informed us about emotion processing?
6 What factors distinguish 'reward' from 'learning' in the study of SEEKING?

6.2 Drawing exercises

1 Label the regions of the triune brain.

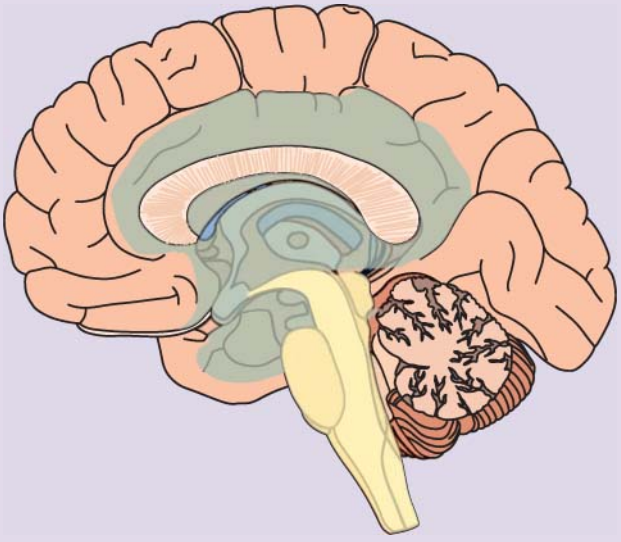


FIGURE 13.23

2 Label the afferent connections to the amygdala.

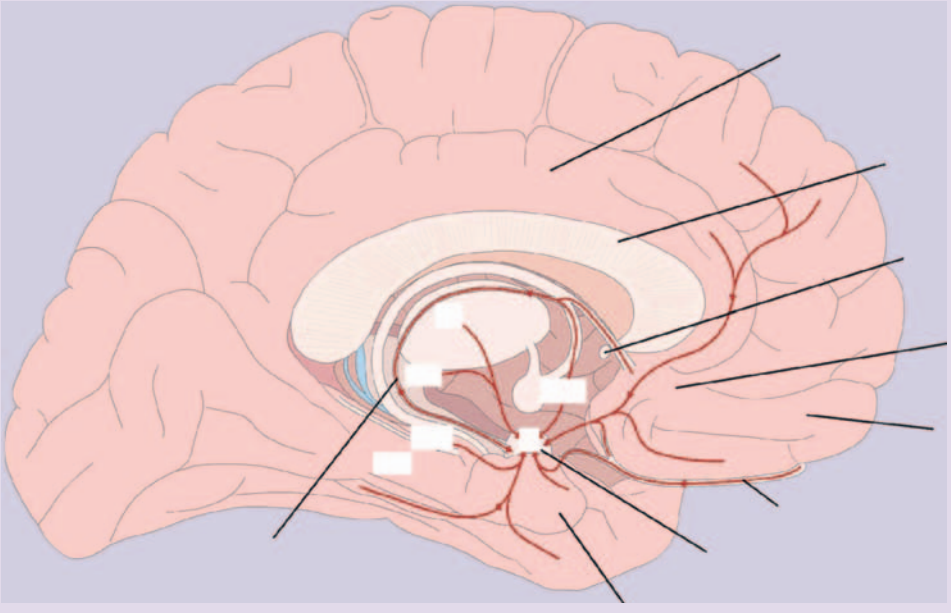


FIGURE 13.24

3 Label the efferent connections from the amygdala.

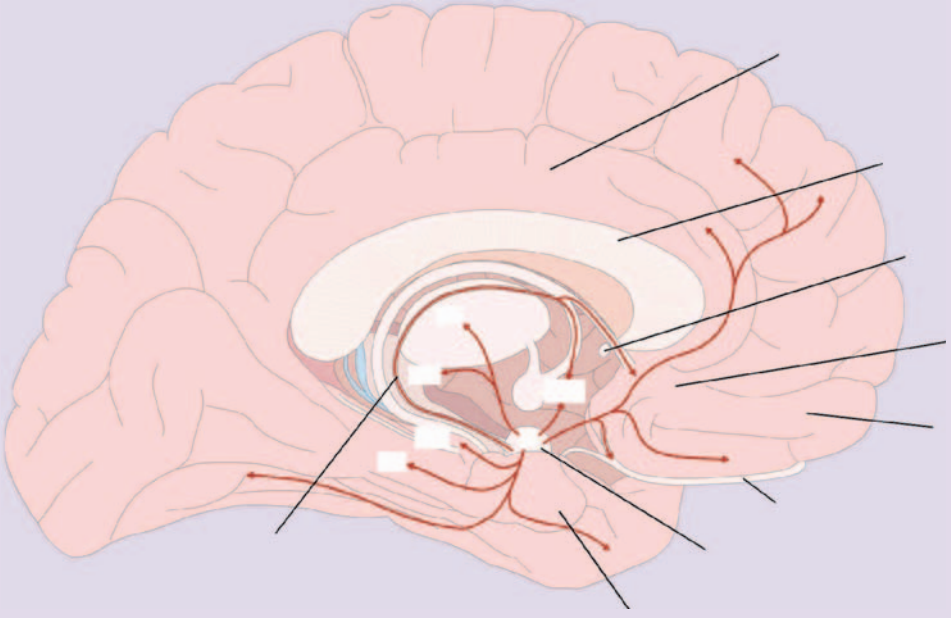


FIGURE 13.25

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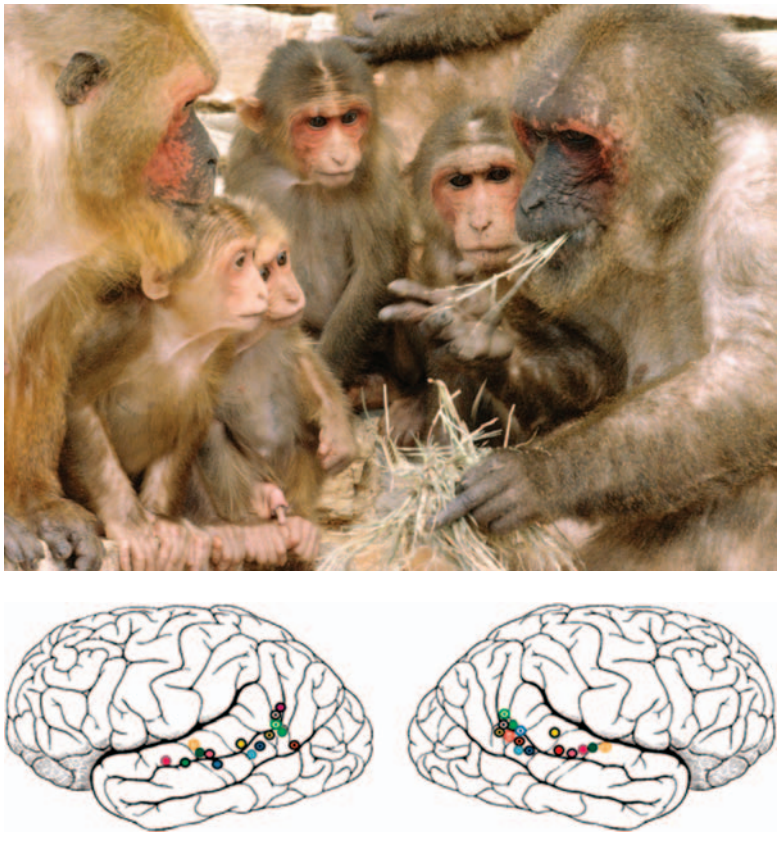
Man is a social animal.

Attributed to Aristotle



If this looks like a scene we could imagine with humans, it is because our social brains have large areas of overlap and similarity with the brains of other primates. The two cortical hemispheres illustrated above show how social cognition often activates the superior temporal sulcus (STS) in the human brain. *Source*: *Top*: de Waal, 2004; *bottom*: Allison *et al*., 2000.

CHAPTER

14

Social cognition: Perceiving the mental states of others

OUTLINE

1.0 OVERVIEW

In this chapter, we will examine one aspect of human cognition that makes us unique among our mammalian relatives – our ability to understand each other as conscious beings with internal mental states. Other mammals have partial abilities to tune into the psychological states of members of their own species, their conspecifics. They can perceive aspects of posture, vocalization, and facial expression as signs and take action based on those signs. Some primates have 'mirror neurons' that appear to allow them to register the commonality between actions of other monkeys and their own actions. However, no other animal has been shown to understand, to make use of, or to depend on the *subjectivity* of other members of its species. It is a peculiarly human ability.

The 'question of other minds' is an old one among philosophers. However, psychological and neuroscientific study of how we understand the mental states of others is more recent. As yet, psychologists and neuroscientists have not agreed on common definitions of the terms that are used to describe and explain social cognition. So a few brief definitions are in order before we begin our study of social cognition.

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

TABLE 14.1 Perspective in social cognition and in science

	First-person perspective	Second-person perspective	Third-person perspective
Data type	Phenomenological data	Empathic understandings	Ordinary empirical data; sense data
Methods of data gathering	Controlled introspection on internal states; traditional psychophysics	Reflection on empathic attunement; internal scanning of emotional and cognitive responses in the presence of another	Objective observation of external objects
Linguistic markers	*I* feel, *I* know	*You* seem, *You* look	*It* is, *S/he* is

1.1 Terms that are used to refer to social cognition

In the research literature, terms that refer to aspects of social cognition are often used interchangeably and in different ways by different researchers.

Empathy carries the sense of feeling the feelings of others. In Latin, the word means 'feeling inside' or 'feeling with'. On the other hand, *theory of mind* (TOM, see Section 1.3) is often used to highlight the idea that we normally have complex metacognitive understandings of our own minds as well as the minds of others – including cognitive and affective aspects. Similarly, Frith and Frith (1999) introduced the term *mentalizing* to capture the idea that, when we have a well-developed theory of mind, we understand ourselves and others not just as sensory objects but also as subjective beings with mental states. We understand others as having mental states that we can anticipate and make use of to guide our own behaviors. *Mind-reading*, like mentalizing, identifies our ability to attune our own behaviors to the minds and anticipated actions of others.

One of the most difficult aspects of understanding the concept of theory of mind is understanding the difference between seeing others as sensory objects versus seeing others as subjective beings with minds and mental states. Having a complete TOM gives us the ability to go beyond the sensory into the mental. We can do things that those with deficient TOMs cannot do. Once we have a TOM we can pretend, lie, deceive, guess, play hide-and-seek, and predict and understand the full range of human emotion. People who have deficits in TOM (people with autism, e.g.) have limited abilities to do these things, as we will see.

Philosophers use the term *intentionality* when they want to speak about how minds and mental states are always '*about* something else' in a way that other physical objects, i.e. body parts, are not. Our thoughts always have an object. For example, we think 'about' the chair, the book, or the idea in a way that our stomach, arm, or tooth are not about anything other than themselves. Minds have mental states; minds *represent* objects and events outside themselves. It is not clear that other species comprehend the intentional nature of minds in their conspecifics. Humans seem to have an implicit understanding of the contents of others' minds.

A separate concept is the psychological term 'intention', our ability to form an image of a goal state and to organize action in pursuit of that goal state. Be careful not to confuse these two very similar terms! Theory of mind abilities allow us to read the intentions of others and to share attention with others about a common focus.

Finally, the term *intersubjectivity* emphasizes our ability to coordinate mutual interactions in light of our perception of the subjectivity and intentionality of others. When this ability is absent, we readily recognize the deficiency in the social exchanges of others. Examples are found in autistic spectrum disorders, in the sometimes deficient emotion recognition of schizophrenia, and in the empathic failures of psychopathic and borderline personalities.

1.2 The importance of perspective: the first, second, and third person

Science usually works from a *third person perspective*. This means that researchers adopt an objective point of view, seeing all evidence as a physical object. Even human beings are seen as objects, as sensory surfaces. The mental 'insides' of human beings are also viewed through objective means such as behavioral observation or brain imagery. Recently, scientists interested in consciousness have begun arguing for an additional way of conducting science that appreciates and accepts data gathered from a *first person perspective*, i.e. using phenomenological data from introspection or self-report. To a certain extent, self-report under controlled circumstances is a well-established scientific

method, for example, in psychophysics and the study of perception.

What about the *second person perspective*? In this stance, the other person is viewed as a *subject* rather than an object, as someone who has mental states. This perspective is less well established in psychological science and neuroscience, although it is well known in philosophy and in clinical psychology. Contemporary social cognition research comes close to examining the second person perspective. To be exact, we are adopting a third person perspective (objective view) on other people as *they* engage in a second person activity.

1.3 Approaches to perceiving others' minds

Once past our fourth birthday (whether we are normally developing or developmentally delayed), we human beings give indications of understanding other minds – 'mentalizing' as Chris Frith has called it. We can recognize and respond to the invisible, internal subjective regularities that account for the behaviors of others. We will call the full-fledged ability to understand and predict our own and others' minds *theory of mind* (TOM). TOM has been explained by three kinds of theories: module theories, theory theories, and simulation theories.

According to *module theories*, such as that of Simon Baron-Cohen, human beings develop a theory of mind module (TOMM) that is separate from but builds on other mental abilities that may be shared with nonhuman primates and other mammals; only humans are presumed to have a complete TOMM. This kind of theory fits well with findings from the study of autism.

Theory theories suppose that TOM capabilities develop as a primitive, implicit theory over the course of development, much like Piaget's conservation theories. Such implicit theories predict abrupt changes in behavior as new knowledge is added, as is seen in the abrupt change in children's understanding of their own minds between ages three and four.

FRONTIERS OF COGNITIVE NEUROSCIENCE

The Social Brain

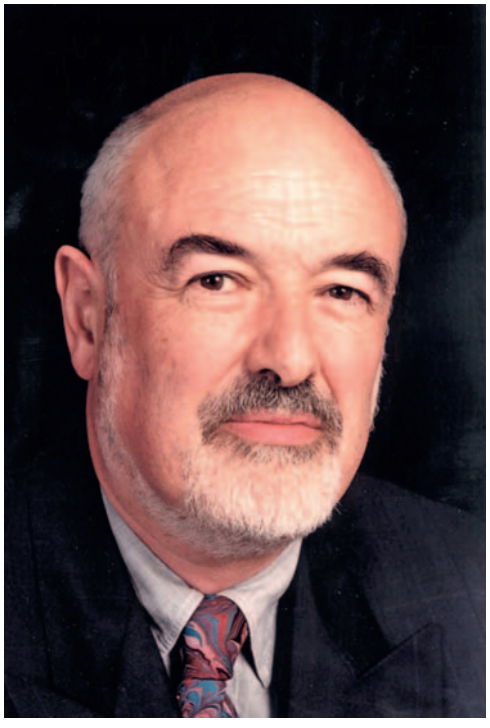


FIGURE 14.1 Christopher Frith, PhD, Wellcome Trust Centre for Neuroimaging, University College London, UK.

The tradition in cognitive neuroscience has been to study people and their brains in isolation, but the past few years have seen a dramatic increase of interest in what happens when people interact with one another. Major buzz-words include *theory of mind:* our ability to read the minds of others, and *mirror neurons*: neurons that respond when we act and also when we see someone else act. For me, the most exciting result from these new studies is the demonstration of how embedded we all are in the social world. We may feel like independent agents, but, in fact, we are constantly being buffeted one way and another by a stream of social signals to which we respond whether we like it or not. Mostly we are not aware that we are responding to these signals.

This idea is confirmed by many experiments, but at the moment I have two favorites that demonstrate such automatic responses. The first (Blakemore *et al.*, 2005) used fMRI to see what happens in the brain when we see someone else being touched. Volunteers were scanned while they saw a video of someone else being touched on the face and also when they were touched on the same spot themselves. The scanning data (Figure 14.2) clearly shows that same region of somatosensory (body touch) cortex was activated whether the participants were touched or whether they saw someone else being

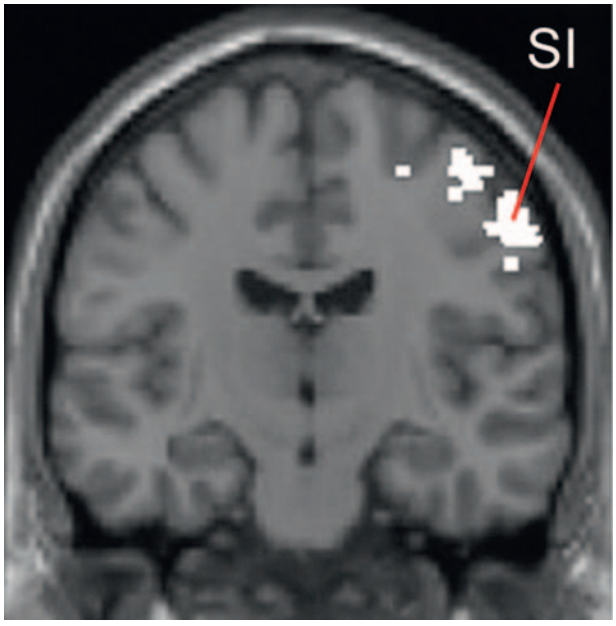


FIGURE 14.2 These brain regions are active when we feel our face being touched and when we see someone else being touched on the face. *Source*: Blakemore *et al.*, 2005.

touched. The location of the activity depended on the precise location of the touch: face or neck, left or right side. The effect did not occur if the participants saw some inanimate object, like a somewhat face-shaped electric fan, being touched. In the vast majority of cases people are not aware that they are feeling someone else being touched. Only in rare cases of synesthesia does the activity break through into consciousness, resulting in reports that 'when I see someone's face being touched I feel it on my own face.'

The second experiment (Liepelt *et al.*, 2009) used the classic psychologist's measure of reaction time. In this study participants had to press buttons with their first or second finger as quickly as possible. The signal to perform this action appeared in a picture of a hand (Figure 14.3). A 1 or a 2 appearing between the first and second fingers of this hand indicated which button to press. The clever feature of this experiment was that, on some occasions, the first and second fingers of the hand in the picture were held down with metal clamps. On these occasions the reaction times of the participants were significantly slower, even though their own hands were completely free at all times. Here

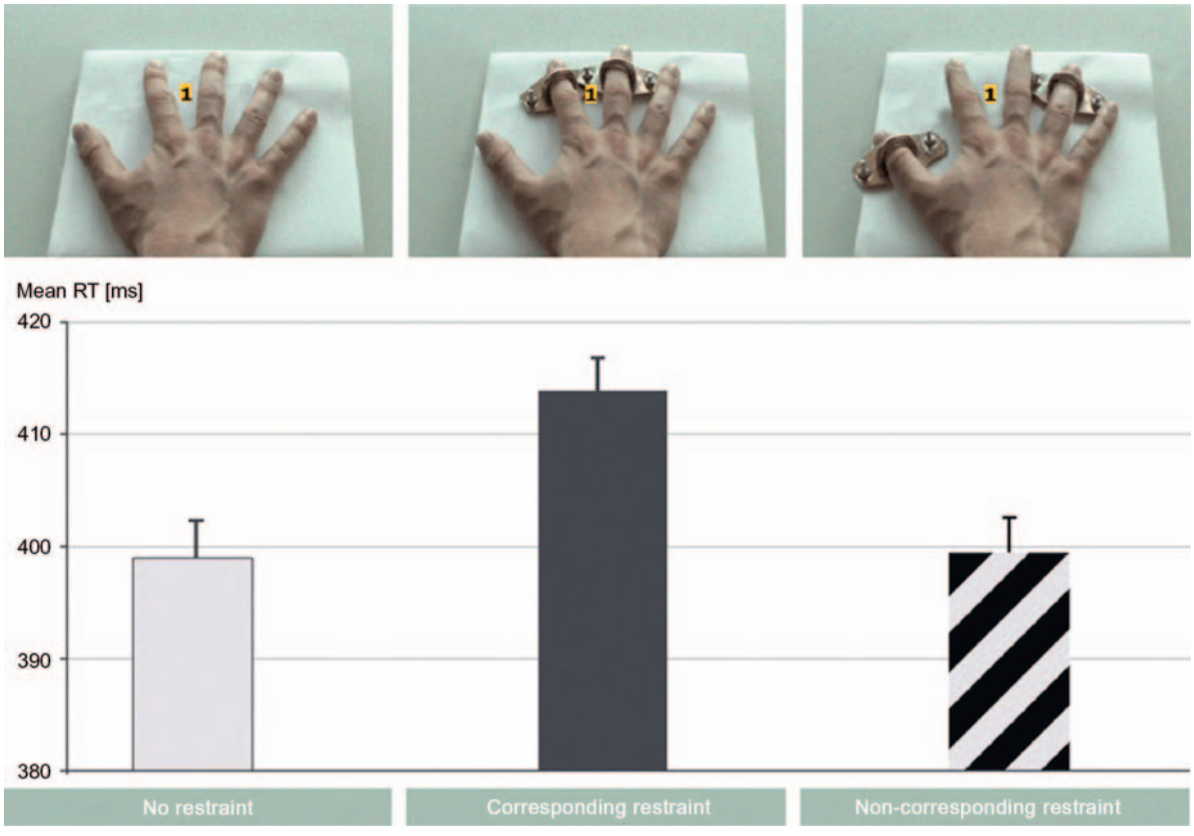


FIGURE 14.3 Experimental design and results for finger responses. *Source*: Liepelt *et al.*, 2009.

again the effect was very specific. Only the fingers that are constrained in the picture were slowed down in the participants.

We are not aware of it, but the mere sight of what is happening to the people around us alters our own feelings and behavior. Perhaps our brain is essentially a social organ.

References

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Liepelt, R., Ullsperger, M., Obst, K., Spengler, S., von Cramon, D. Y., & Brass, M. (2009). Contextual movement constraints of others modulate motor preparation in the observer. *Neuropsychologia*, *47*(1), 268–275.

Simulation theories suppose that we understand other minds by internally simulating or 'running off line' the mental states of others in each situation. The dual responsiveness of mirror neurons to self- and other-generated action could be taken as support for simulation theory.

It seems very likely that all three kinds of theories are needed to account for human 'mentalizing' abilities. As we will see, there are separable skills that develop in mammals and humans that operate much like *modules*; we can lose one module but still have the other. The system that allows us to imitate others seems to operate through *internal simulation* of the actions of others. Finally, adult human beings have sophisticated social perception abilities that allow us to reason about other people's internal states; we act as if we have a complex set of rules about our own and others' mental states that could be called an *implicit theory*.

2.0 AN ORGANIZING FRAMEWORK FOR SOCIAL COGNITION

Simon Baron-Cohen (1995) hypothesized that a fully developed theory of mind is composed of four kinds of skills that develop independently. These skills are *detection of intentions of others, detection of eye-direction, shared attention*, and a complex repertoire of implicit knowledge about others, which he called the *theory of mind module*. Some of these skills are observed in mammals and non-human primates as well as in humans. However, only the theory of mind module appears in normally developing human beings. We will first introduce Baron-Cohen's model (summarized in Figure 14.4) and then use it as a way to organize the larger body of social cognition research.

2.1 Intention

The first component of Baron-Cohen's TOM is called the *intentionality detector* (ID). This is the ability to perceive intention or purposeful action in many forms of biological and non-biological movement. For example, when we watch leaves swirling in a parking lot, we have a tendency to see the leaves as 'wanting to go together'. We ascribe common purpose to the pile of leaves. Or, when we watch pieces of modeling clay being moved around an artificial landscape in claymation films, we readily attribute intentions and other mental states to the pieces of clay. Likewise, when we watch people and animals engaged in behaviors, we seem to understand their goals and the desired outcomes of their actions. We interpret *action* as intention.

2.2 Eye detection

The second component of the model is the *eye direction detector* (EDD), the skill to detect eyes and eye-like stimuli and to determine the direction of gaze. Many mammals seem to have the ability to notice and use information about eye direction. Cats, for example, use eye direction as part of their social dominance behavior with other cats; the non-dominant cats must avert their eyes in the face of the dominant cat. Humans, from the first hours of life, search for and focus on the eyes of their caregivers. We also have a strong tendency to see non-living stimuli as eye-like; hence, we see the 'man in the moon' and faces on automobiles, gnarled trees, and mountains. The 'language of the eyes' seems to be a fundamental means of communicating mental states among humans.

Both the intentionality detector and the eye direction detector involve *dyadic* (two-way) interactions. That is, there is *one perceiver* and *one object of perception*. As yet, no sharing of mental states is necessarily involved. Both EDD and ID are found in non-humans as part of their social perception abilities. It is the third module of TOM that is unique to human social cognition.

2.3 Shared attention

The *shared attention mechanism* (SAM) is the ability we have, by the end of our first year of life, to understand that when someone else shifts his or her direction of gaze

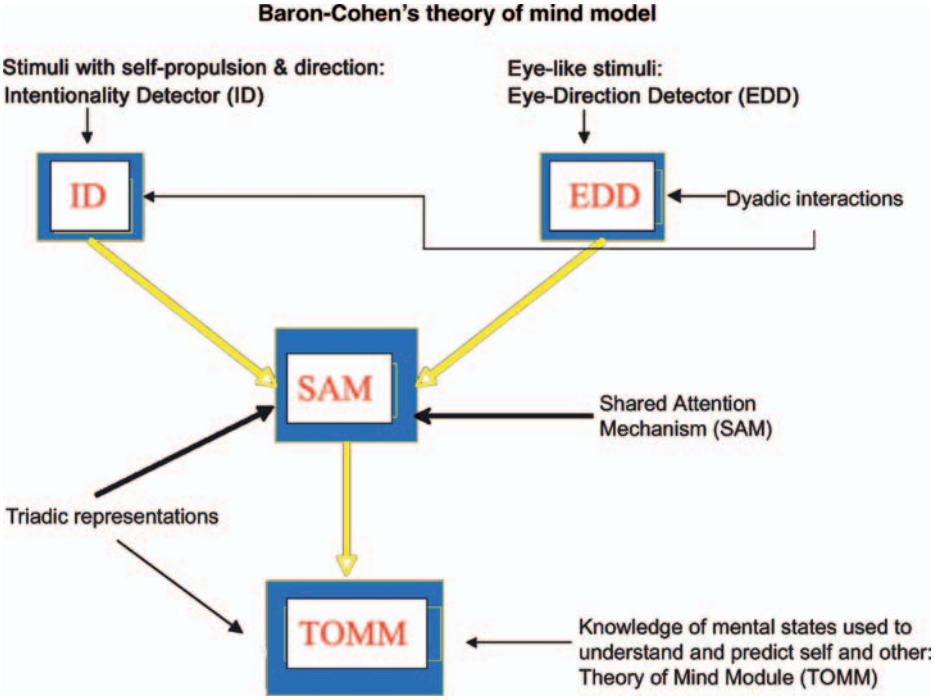


FIGURE 14.4 A schematic diagram of Baron-Cohen's theory of mind model with the eye-direction detector (EDD), shown on the upper right, sending inputs to the intentionality detector (ID), upper left, and to the shared attention mechanism (SAM), shown in the center of the diagram. The SAM also receives inputs from the ID and interacts with the theory of mind module (TOMM). *Source*: Adapted from Baron-Cohen, 1995.

he or she is 'looking at' something. We seem to learn that looking leads to seeing – an advance over the simpler signal of eye direction. We realize that we can look too and see the same thing. Gaze shifting and social pointing of fingers are ways we learn to direct the attention of a companion.

Infants before 1 year of age, most other primates, and other mammals do not have a shared attention ability. We can see this in our much loved companion animals. While our family dog may chase a ball and bring it back, he will not follow our gaze if we look toward a ball lying in the grass. He will not follow our pointing finger when we try to direct his gaze toward the ball. The dog has considerable intelligence but does not have shared attention. Similarly, an infant at 6 months does not turn her head to follow the caregiver's gaze; a 1-year-old does. Shared attention abilities mark the human species.

2.4 Higher-order theory of mind

The final component of full-fledged theory of mind is what Baron-Cohen has called the *theory of mind module* (TOMM), a complex knowledge base containing rules of social cognition that develops by the time we reach our fourth birthday. TOMM tells us that:

- Appearance and reality are not necessarily the same – a rock can look like an egg but not be an egg; I can pretend to be a dog but not be a dog
- A person who is sitting still in a chair may be 'doing something', i.e. thinking, imagining, or remembering (young children do not appreciate this)
- Other people can have mental states as well as physical states
- Other people can know things that I don't know; I can be fooled or deceived; I can detect deception
- I can know things that other people don't know: I can fool or deceive others; I understand the point of games like hide-and-seek
- My mental state in the past was different from how it is now
- Facial expressions are indicators of mental states as much as they are indicators of physical states; I can distinguish a surprised face from a yawning one.

TOM is not the same as intelligence or IQ. Developmentally delayed children and adults display complete TOM abilities despite low IQs, while people living with autistic spectrum disorders (ASD) may have high IQs but markedly deficient TOM abilities.

We can now use Baron-Cohen's four TOM skills as a way to organize and guide our study of social cognition.

3.0 MIRROR NEURONS AND INTENTION DETECTION

Where is social cognition located in the brain? Some recent investigations of mirror neuron systems in the

macaque monkey have brought to light some dramatic findings regarding where social and intentionality systems may be processed in the brain. Initial studies using neuroimaging techniques such as fMRI to investigate a possible similar system in humans provided intriguing new evidence that such a system may exist. More recent studies, however, cast a shadow on earlier findings. Existence of a human mirror neuron system is still an open and hotly debated topic in the field of social cognitive neuroscience. We begin our discussion with findings for the macaque monkey and then review the evidence for mirror neurons in a human brain.

3.1 From action to intention

The *mirror neuron system* (MNS) is a collection of cortical neurons that is theorized to allow one to understand the intentions of others from observation of their actions. Mirror neurons were first discovered in the frontal cortex of macaque monkeys and shortly thereafter in their parietal cortex. These cortical neurons have the remarkable property that the individual mirror neuron fires not only when a particular action is perceived but also when the observer performs the same action. Immediately, researchers grasped the possibility that mirror neurons might be a means of comparing one's own actions with those of others. In addition, mirror neurons are being examined as a basis for inferring the goals and intentions of others through internal matching of action representations of others' actions with action representations in one's own action repertoire.

The original work on mirror neurons was conducted by Rizzolatti *et al*. at the University of Parma in Italy in the early 1990s. They found mirror neurons in the frontal motor area of monkey cortex in an area labeled F5. Using single-cell recordings of macaque cortical neurons, they found that such neurons would respond when the experimenter grasped peanuts placed on a board as well as when the monkey grasped the peanuts; the neuron did not respond when the peanut was observed alone on the board or when the experimenter grasped the peanut with a tool. Clearly, the act of grasping food with one's hand was the act that the neuron was 'tuned' to. Figure 14.5 illustrates a monkey with a microelectrode apparatus affixed to his head; he is sitting in a functional magnetic resonance imaging (fMRI) recording apparatus. Figure 14.6 shows the experimental arrangement for assessing responses of single mirror neurons in different conditions used by Rizzolatti and his colleagues.

To insure that the single-cell recordings were not an artifact of monkey-experimenter interaction or

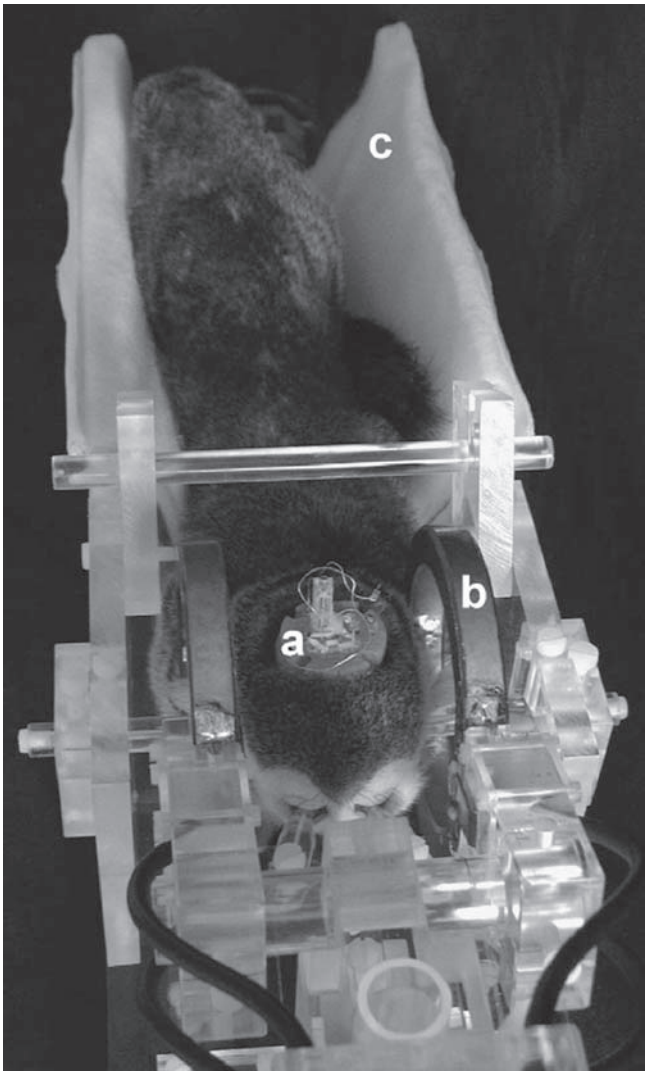


FIGURE 14.5 Monkey with a microelectrode attached to his head, performing inside an fMRI apparatus. a, microelectrode; b, fMRI coil; c, cradle. *Source*: Tammer *et al*., 2006.

food expectancy, the researchers also recorded from the monkey while it observed nearby food grasping actions between the experimenter and a second monkey. The mirror neuron responded as before, i.e. it responded when the observed monkey grasped the food, not when the food was moved, but again when the observed monkey grasped the food (Figure 14.7).

Research with macaque monkeys has been done with single-cell recordings of individual prefrontal neurons. The existence of mirror neurons in macaques is well established. Similar single-cell recordings of neurons have not been conducted in humans; evidence for the human mirror neuron system (MNS) comes from imaging data that aggregates the activity of many

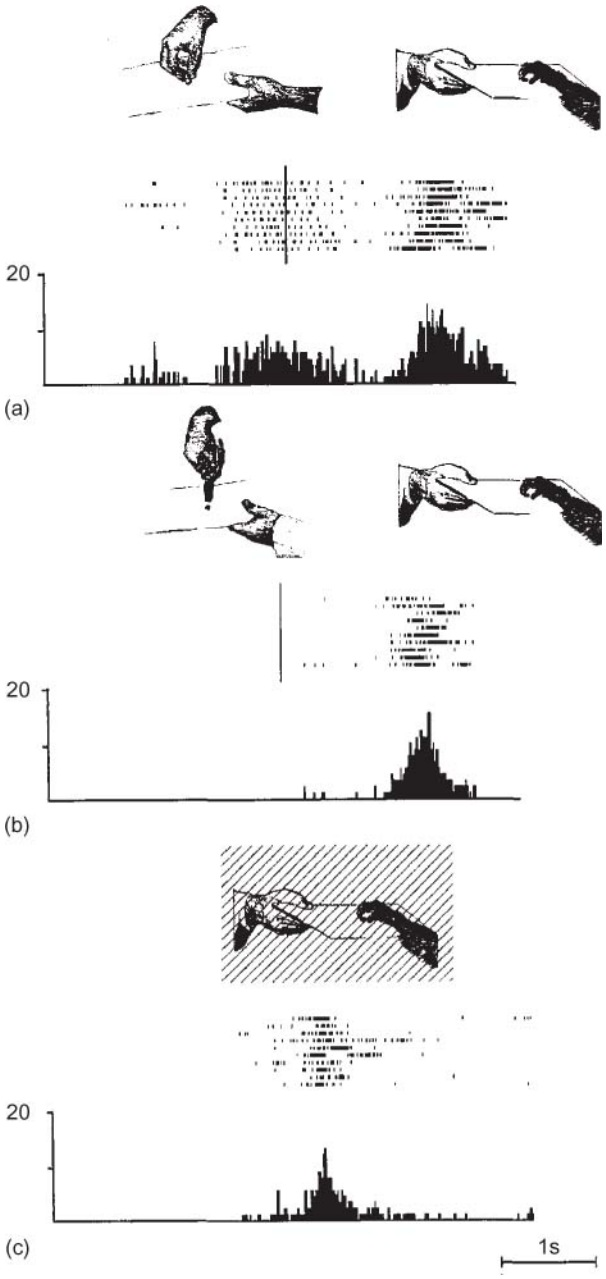


FIGURE 14.6 The observed acts and single-cell responses of mirror neurons. (a) The experimenter places a piece of food on the board, moves it toward the monkey, and the monkey grasps the food. The figure at the top of the panel illustrates the acts. Individual responses of the neuron over time are presented in the middle of the panel. At the bottom is a histogram representing the total responses in each 20-millisecond time segment over time. Notice the numerous responses when the experimenter grasps the food, the lack of responses while the board is moved, and the numerous responses again when the monkey grasps the food. (b) The experimenter grasps the food with a tool, moves the food toward the monkey, and the monkey grasps the food with its hand. Notice here that responses occur only when the monkey's hand grasps the food. (c) The monkey grasps the piece of food in the dark. Notice the numerous responses to the grasping act even when it is conducted in the dark. *Source*: Rizzolatti *et al*., 1996.

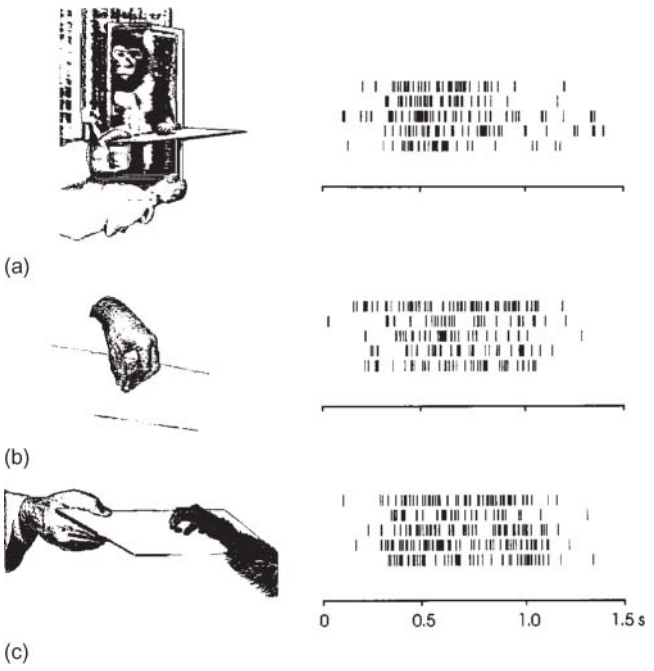


FIGURE 14.7 Observed acts of another monkey can evoke mirror neuron responses. The mirror neuron responds to observed action of another monkey (a), of the experimenter (b), and of the recorded monkey itself (c). *Source*: Rizzolatti *et al*., 1996.

neurons. Thus, individual human mirror neurons have not been studied to date. Nevertheless, there are marked similarities between mirror neuron systems studied in monkeys using single unit recordings and in human using neuroimaging of population-level neuronal responses. Rizzolatti *et al*. (2002) have summarized the monkey to human homologies in Figure 14.8.

Area F5 in the macaque (purple in Figure 14.8) and Brodmann area 44 in humans (pink) seem to code for hand actions, such as those studied in the original mirror neuron research. Area F4 in the macaque and the ventral premotor cortex (vPM or lower Brodmann area 6 in humans (colored red in Figure 14.8) both respond to arm and wrist movement. Individual frontal neurons in the macaque and prefrontal areas in humans are tuned to arm and wrist movements toward particular locations in the space around the individual. This implies that mirror neurons in these areas are not simply representing general movements of the arm and wrist, but rather they are responding to acts connected to particular goals, i.e. reaching locations in space.

Note: you may remember that Brodmann area 44 in the left hemisphere has been called *Broca's area*. It has traditionally been seen as the cortical speech area. Recent studies of imitation in humans have shown that Brodmann area 44 has mirror neuron

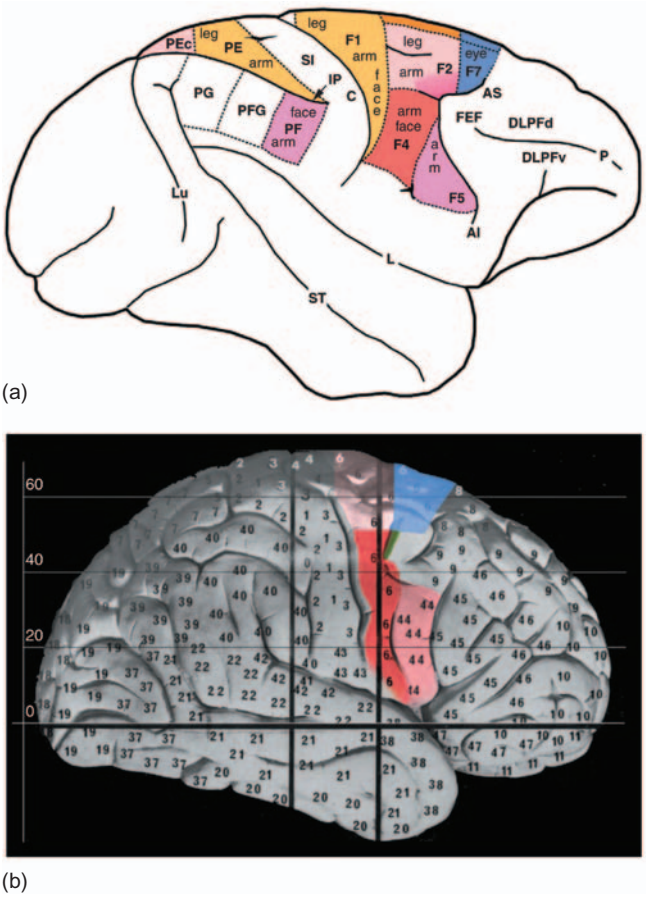


FIGURE 14.8 Monkey to human homologies in mirror neuron locations and functions. (a) A lateral view of the macaque right cortex. (b) A lateral view of the human right cortex. *Source*: Rizzolatti *et al*., 2002.

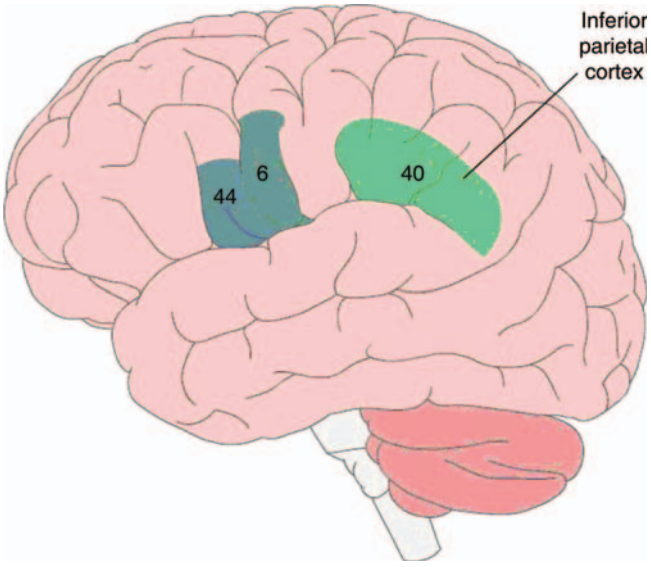


FIGURE 14.9 A simplified view of the left hemisphere with locations of the theorized frontal mirror neuron system highlighted. (Note: Inferior parietal cortex = supramarginal gyrus = Brodmann area 40; ventral premotor cortex = lower Brodmann area 6; posterior inferior frontal gyrus = pars opercularis of IFG = Brodmann area 44.)

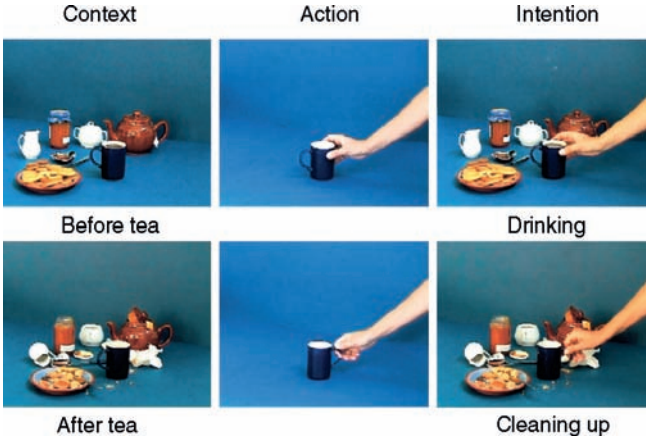


FIGURE 14.10 Two different contexts, acts, and intentions used in Iacoboni *et al*. (2005): drinking tea versus cleaning up after tea. Left panel shows the stimuli in the Context condition, center panel shows the Action condition, and right panel shows the Intention condition. *Source*: Iacoboni *et al*., 2005.

capabilities, involving representation of actions with the hand and arm (Iacoboni, 2005; Figure 14.9). Thus, Broca's area has mixed abilities.

A long-standing challenge in the study of mirror neurons has been distinguishing between simple *action recognition* (is that grasping, reaching, or holding?) and *intention detection* (where an agent has a goal which is accomplished by the action: drinking tea versus cleaning up after tea). The final piece of evidence linking mirror neurons to intention detection comes from studies of human acts carried out in different contexts. A central question in these studies is: does the MNS respond to the act regardless of context or does it respond to acts in particular contexts? The first alternative implies that mirror neurons do action recognition. The second allows us to extend the inference: MNS is for intention detection.

Marco Iacoboni and his colleagues have obtained evidence supporting the argument that the MNS responds to intentions rather than particular actions by examining fMRI images as participants observe acts with and without context. They found that actions embedded in contexts (Intention in Figure 14.10), compared with the other two conditions (Context only or Action), yielded a significant fMRI increase in the posterior part of the inferior frontal gyrus and the adjacent sector of the ventral premotor cortex where hand actions are represented. In order to demonstrate that intention could be assessed separately from

action, the researchers compared fMRI images from the two intention and action conditions. These comparisons are shown in Figure 14.11.

Follow-up studies by Dinstein and colleagues (2007, 2008) and Caramazza and colleagues (2009), however, have not supported these earlier findings. Dinstein and colleagues (2008) found that while areas in the parietal lobe (the anterior intraparietal sulcus) were active for perception and execution of movements, the pattern of activity differed sharply depending on whether the movement was observed or executed (see Figure 14.12 for an illustration of their experimental design). Dinstein and colleagues suggested that these results indicate a differing subpopulation of neurons were supporting the observation versus execution of movements (Figure 14.13).

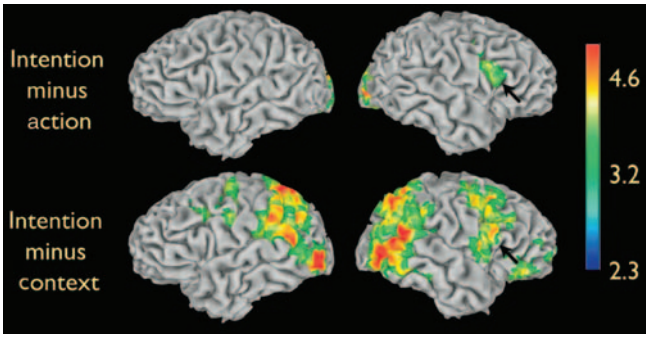


FIGURE 14.11 fMRI results from Iacoboni *et al*. (2005). Upper panel shows response in the Intention minus Action conditions; lower panel shows Intention minus Context conditions. *Source*: Iacoboni *et al*., 2005.

A related study by Caramazza and colleagues (2009) provided related evidence in an fMRI study investigating adaption of neurons within brain areas suggested to hold mirror neurons. They found that these brain areas adapted when hand gestures were observed, but not when they were executed.

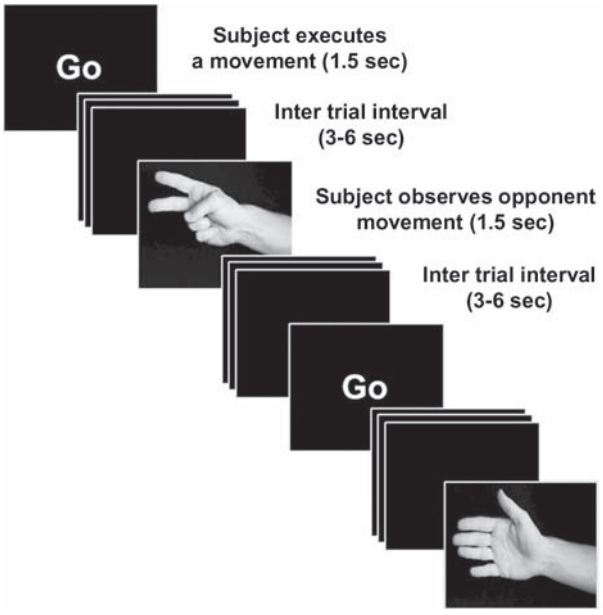


FIGURE 14.12 The experimental paradigm used in Dinstein *et al*., 2008. The subjects played a version of 'rock, paper, scissors' in the scanner. When the subject sees the word 'GO' at the beginning of the trial, he executes a game movement (hand gesture for 'rock', 'paper', or 'scissors'). After a brief (3-6 s) delay, he then observes his opponent's movement. This was repeated for 36 executions and 36 observations. *Source*: Dinstein *et al*., 2008.

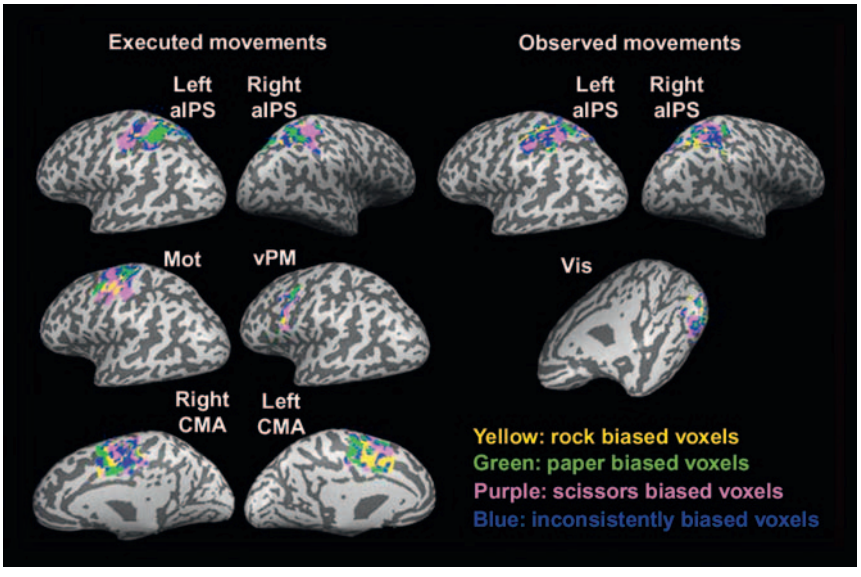


FIGURE 14.13 Brain activity for executed versus observed movements. The results from the Dinstein *et al*., 2008 'rock', 'paper', 'scissors' study show that differing brain areas are activated for executing versus observing closely matched hand movements. These findings argue against some theories of the human mirror neuron system.

TABLE 14.2 Ethological review of eye/gaze processing across classes of animals

Subject group	Eye presence	Simple gaze	Gaze following	Joint attention	Mental attribution
Fish	✓	?	?	?	?
Reptiles	✓	✓	?	?	?
Birds	✓	✓	?	✓(?)	?
Rodents	✓	?	?	?	?
Dogs (domestic)	?	✓	✓	?	?
Prosimians	?	✓	X	?	?
Monkeys	✓	✓	✓✓	✓	X
Great apes	✓	✓	✓	✓	X (?)
Human					
– 6 months	✓	X	X	X	X
– 9 months	✓	✓	X	X	X
– 12 months	✓	✓	X	✓	X
– 18 months	✓	✓	✓	✓	X
– 24 months	✓	✓	✓	✓	X
– 48 months	✓	✓	✓	✓	✓
– Autism	✓ (?)	✓	?	X	X
– Down syndrome	✓	✓	✓	✓	✓
– Schizophrenia	✓	✓	?	?	?
– Amygdala damage	✓ (?)	X	X (?)	?	X (?)

(from Emery, 2000)
✓ = positive evidence; X = no evidence; ? = not tested or controversial evidence

Cumulatively, these and other recent studies of the human MNS are providing evidence that the processes of observing and executing a motor act do not bear as many similarities across human and macaque brains as initially thought. Studies of the MNS are a good example of how scientific theories develop and change through ongoing experimentation, with new and revised hypotheses tested as the experiments and the theory are refined and improved.

3.2 Eye detection and gaze perception

Perception of eyes in conspecifics and guiding of social behavior in light of that perception occurs in many classes of animals from reptiles to humans. A clear understanding of the role of the eyes in social cognition requires that we understand the various kinds of eye and gaze processing that have been studied. In a review of literature including numerous animal classes, Emery (2000) showed an evolutionary trend in complexity of gaze processing. Table 14.2 summarizes Emery's findings.

While fish, reptiles, birds, and other mammals have some ability to process eye-like stimuli (horizontal pair of dark circles) and perceive gaze direction, only great apes (gorillas, chimpanzees, bonobos, and orang-utans) and humans have shared attention and can use the 'language of the eyes' to understand mental states of others.

Several types of eye and gaze processes are shown in Figure 14.14. Where do these processes take place in

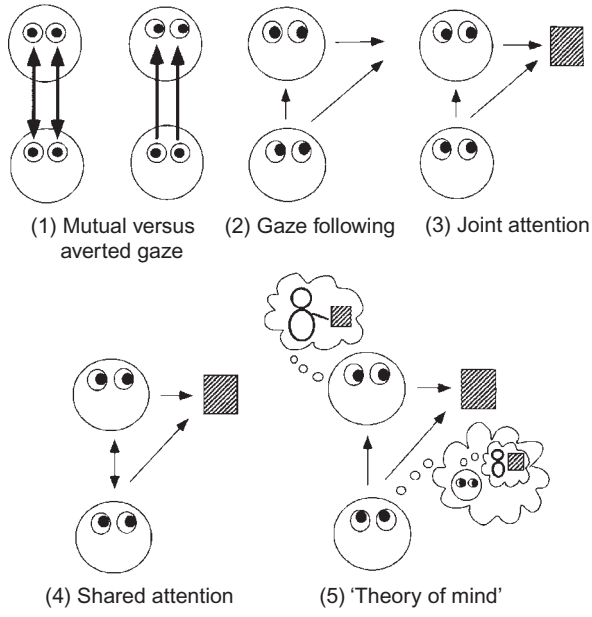


FIGURE 14.14 Eye and gaze processing. (1) Mutual gaze is where the attention of individuals A and B is directed to one another. Averted gaze is when individual A is looking at B, but the focus of B's attention is elsewhere. (2) Gaze following is where individual A detects that B's gaze is not directed toward them and follows the light of sight of B to a point in space. (3) Joint attention is the same as gaze following except that there is a focus of attention (an object) so that individuals A and B are looking at the same object. (4) Shared attention is a combination of mutual attention and joint attention, where the focus of attention of A and B is on an object of joint focus and on each other ('I know you're looking at X and you know that I'm looking at X'). (5) Theory of Mind relies on 1–4 as well as higher order social knowledge that allows individuals to know that the other is attending to an object because they intend to do something with the object. *Source*: Emery, 2000.

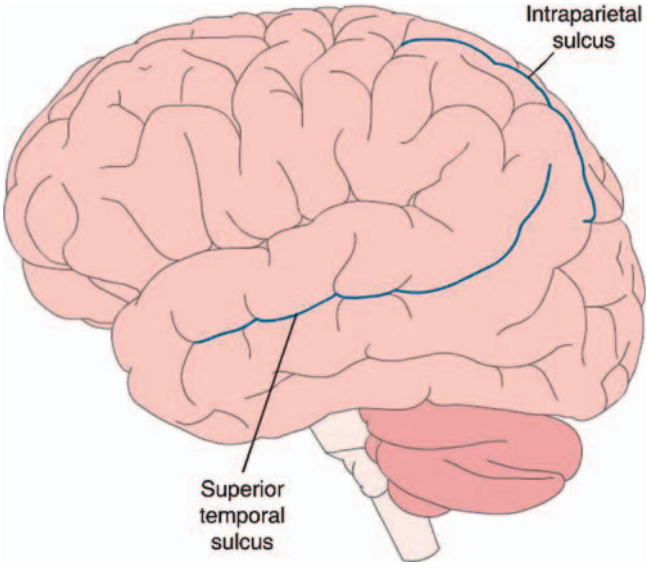


FIGURE 14.15 Superior temporal sulcus and intraparietal sulcus: eye and gaze detection areas.

the brain? The superior temporal sulcus registers eyes and eye-like stimuli. The more complex levels of gaze processing (gaze direction and detection of gaze aversion) involve connections between STS and areas in the parietal lobe, particularly the intraparietal sulcus (IPG; Haxby *et al*. 2000) (Figure 14.15). In addition, connections of STS and IPG with subcortical structures, such as the amygdala, allow us to register the social and emotional significances of gaze, including threat.

Social information from eyes and gaze direction come from the *changeable aspects of the human face*. We can also use visual information to detect the *invariant aspects of individual faces*, such as identity. These aspects of face perception occur in a separate area of the temporal cortex discussed in a section later in this chapter.

Finally, attribution of mental states involves connections of the STS to the MNS and to medial frontal cortical areas (Iacoboni, 2005). We will discuss attribution of mental states in greater detail shortly.

3.3 Shared attention

Shared attention seems to be a social skill that is unique to great apes and humans. Remember shared attention is more than simply looking at the same thing that another person is looking at. Shared attention involves the additional qualification that the two observers not only observe the same object but also know that the other is looking at the object. It is a triadic (three-way) activity. Shared attention allows us implicitly to recognize that: '*I* know that *you* are looking at *that*'. Apes and humans seem to know that when conspecifics are gazing at something, they are also internally representing it. Looking leads to seeing. If I want to see what you see, I can follow your gaze (see Box 14.1).

BOX 14.1 Gaze-following experiment

Try this experiment with shared attention: when you are in a gathering of friends or classmates, shift your gaze to the corner of the room without saying anything. See whether others follow your gaze. Ask them why they did what they did.

FIGURE 14.16 An 18-month-old pointing. Pointing is a sign of triadic interaction. *Source*: Brooks and Meltzoff, 2003.

How do these shared processes get set up in humans? Brooks and Meltzoff (2003) have shown that human infants begin to follow the direction in which an adult turns his or her head by the age of 9 months; however, at 9 months, the infant follows head direction whether the model's eyes are open or closed. By 12 months of age, the infant will follow gaze more often when the model's eyes are open that when they are shut. The infant follows gaze rather than head direction now. Shared attention has developed. The infant seems to know implicitly that open eyes allow looking; looking leads to seeing (Figure 14.16).

What areas of the brain support shared attention? We know that STS supports eye detection. In order to move from simple detection to shared attention, areas in the prefrontal cortex become involved. Williams and colleagues (2005) studied adults when they were experiencing shared attention compared to a control condition (Figure 14.17).

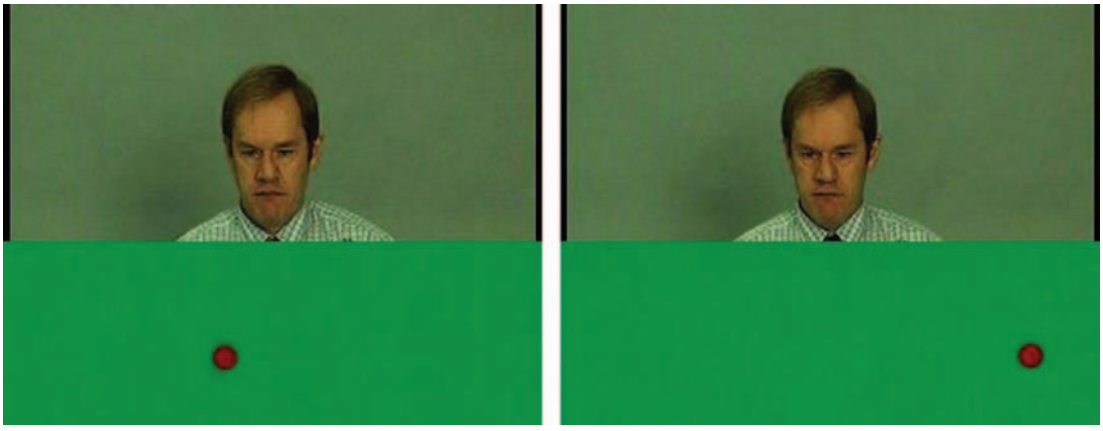


FIGURE 14.17 Stimuli used to create joint attention. When we look at the red dot on the left, we have the sense that the man is looking at the same object as we are; looking at the red dot on the right does not lead to the same sense of shared attention.*Source*: Williams *et al*., 2005.

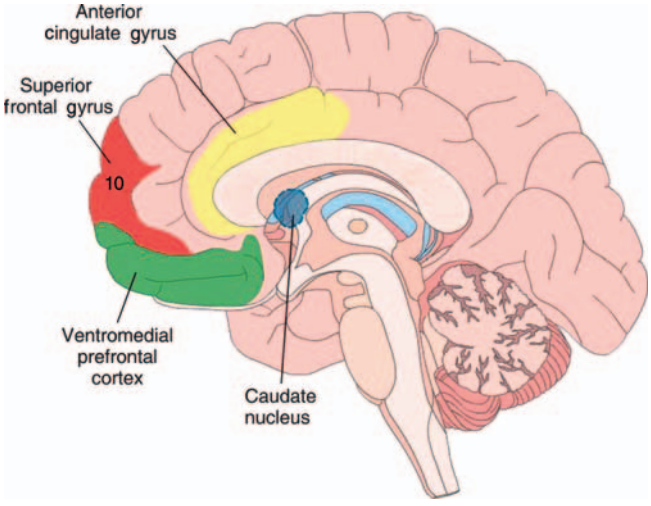


FIGURE 14.18 Networks for shared attention.

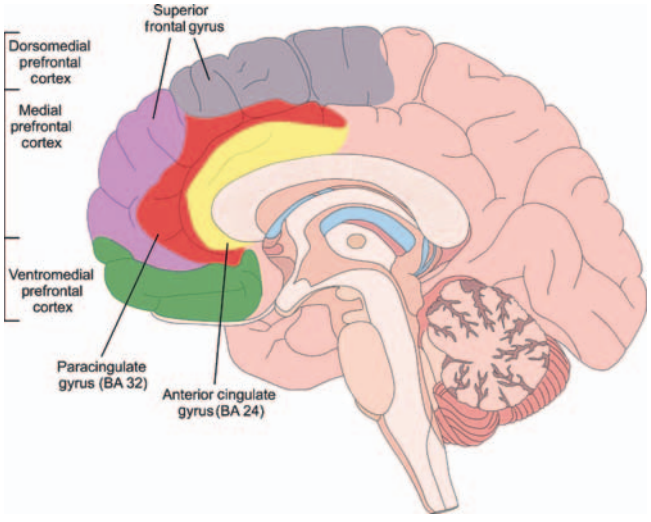


FIGURE 14.19 Divisions of prefrontal cortex: DM-PFC, M-PFC, and VM-PFC. Superior frontal gyrus, cingulate (BA 24), and paracingulate (BA 32) are areas shown to be important in attribution of mental states.

Images from fMRI analyses show that shared attention recruits frontal areas including the ventromedial prefrontal cortex (VM-PFC), the left superior frontal gyrus (BA 10), cingulate gyrus, and caudate nucleus. The VM-PDF is associated with registering the mental state of the other as we will discuss next. Williams and colleagues speculate that BA 10 is responsible for matching perception and action (Figure 14.18).

3.4 Higher-order TOM abilities

3.4.1 Attribution of mental states to ourselves and others

In the previous sections, we found that the paracingulate is involved in imitation learning and that the ventromedial prefrontal cortex (VM-PFC) is involved in shared attention. In this section, we will examine the role that the medial wall of the PFC plays in attribution of mental states to others, or, as Chris Frith calls it, 'mentalizing'.

The medial wall of prefrontal cortex can be divided into three segments from top to bottom: dorsomedial prefrontal cortex (DM-PFC), medial prefrontal cortex (M-PFC), and ventromedial prefrontal cortex (VM-PFC). (They are divided by convention according to their Talairach coordinates in three-dimensional space, which we will not worry about here.) DM-PFC includes the cortex at the top of the medial wall of the prefrontal cortex. M-PFC is the middle section of the medial wall of PFC. VM-PFC is composed of the bottom of the prefrontal lobe and the lower inside wall of the prefrontal cortex (Figure 14.19).

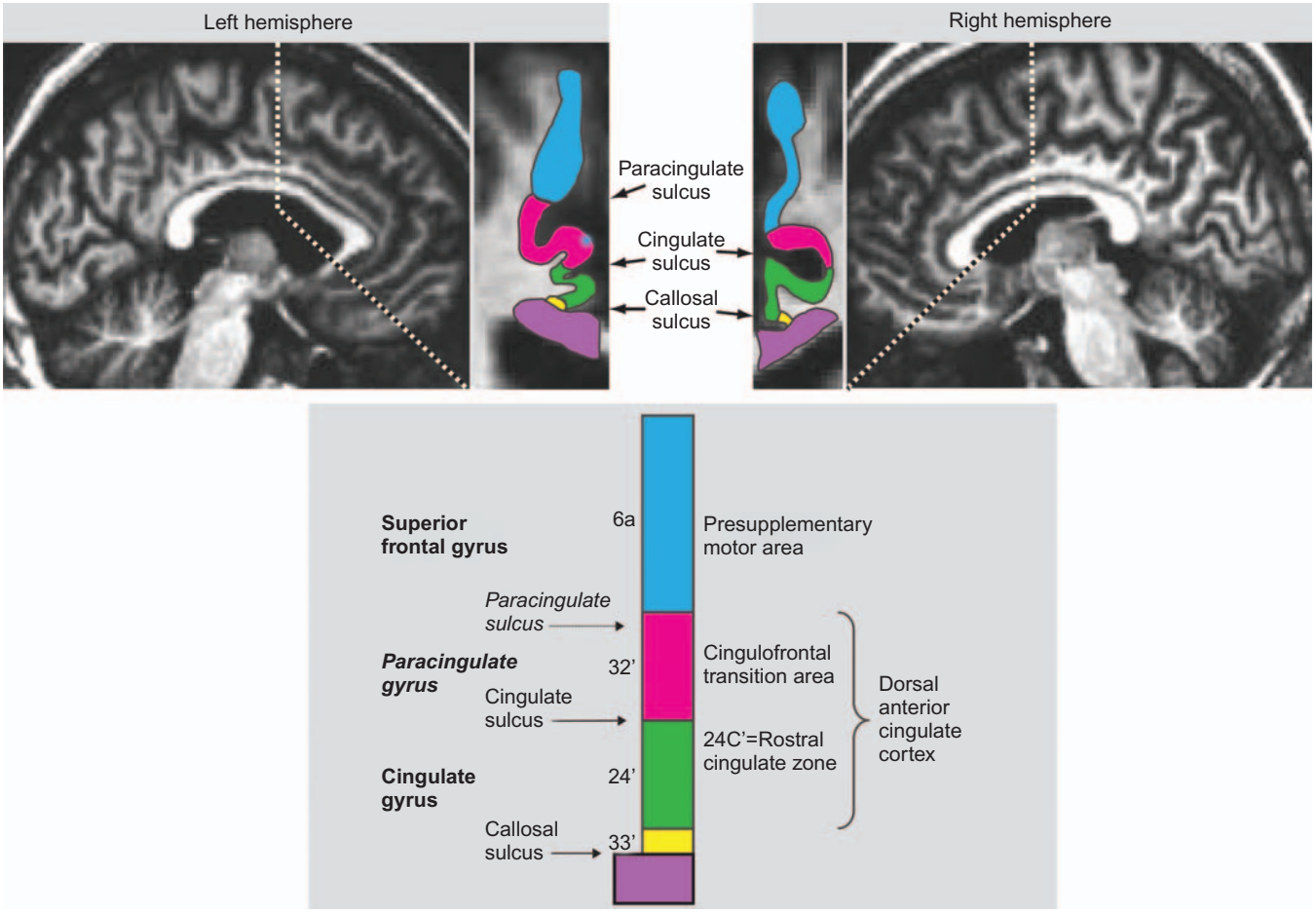


FIGURE 14.20 Anatomy of cingulate and paracingulate gyri: the upper left panel shows the left hemisphere, and the upper right panel shows the right hemisphere. The paracingulate sulcus is shown in blue, the cingulate sulcus is shown in pink, and the callosal sulcus is shown in purple. Lower panel shows these regions in more detail, including the rostral portion of the cingulate zone. *Source*: Heckers *et al*., 2004.

The cingulate and paracingulate gyri, which are sometimes spoken of collectively as the anterior cingulate cortex (ACC), form a belt (*cingulum* in Latin) around the corpus callosum. In addition, depending on how the gyri of individual brains are folded, the paracingulate gyrus may be folded into a sulcus. Figure 14.20 helps us see the anatomy of the cingulate and paracingulate gyri. Figure 14.21 depicts brain areas active for perspective taking and intentional stance.

3.4.2 Perspective taking and intentional stance

Perspective taking is a social skill that is fundamental to human empathy. It allows us to understand how another person thinks and feels about a painful situation. For example, when people are asked to imagine the pain that they or another person would feel (compared to how an artificial limb would feel) when their fingers are pinched in a car door, the medial prefrontal cortex is significantly activated as well as other cortical areas associated with pain perception (Jackson *et al*., 2006). Specifically, the paracingulate (BA 32) cortex of the M-PFC is significantly activated in both perspectives; it registers imagined self and other pain. In addition, when participants were imagining their own pain, the cingulate cortex (BA 24) was also active. This difference reflects our ability to empathize with the pain of others but also to distinguish our own pain from theirs.

Or consider playing a game with another: gamers and athletes speak of 'psyching out' their opponent. A lot of what they mean is that they read the other person's mind. To do this, we put ourselves in the other person's shoes or, to say it another way, we use empathy. When we play the game 'Rock, scissors, paper' against an unseen person (compared to an unseen computer), we adopt an intentional stance – we act as if the opponent is another subjective being.

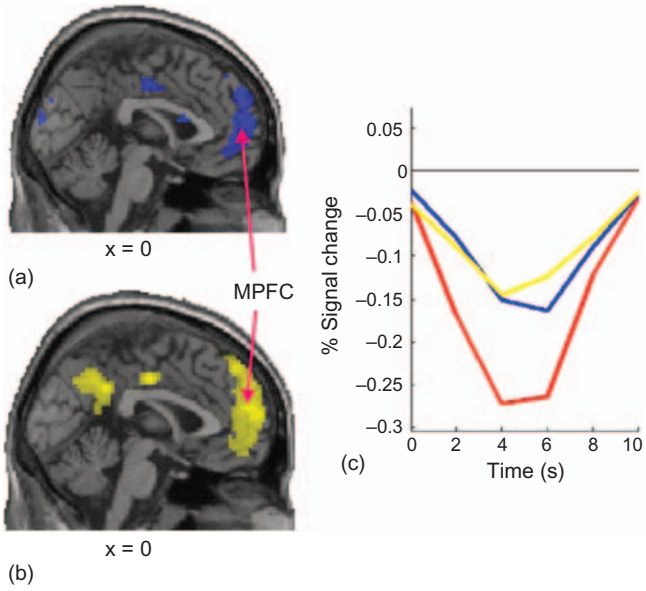


FIGURE 14.21 Perspective-taking and intentional stance. (a) Significant medial prefrontal activation for self versus artificial pain. (b) Significant M-PFC activation for other versus artificial pain. (c) Change in regional blood flow in the PET procedure in M-PFC; self = blue line; other = yellow; artificial limb = red. *Source*: Jackson *et al.*, 2006.

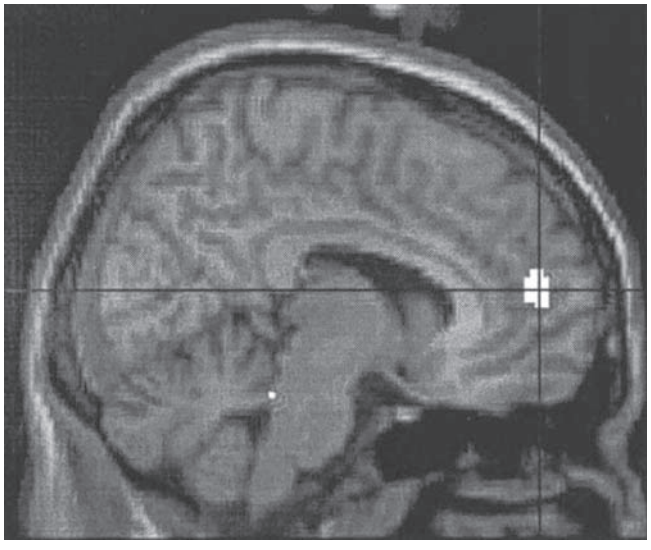


FIGURE 14.22 Activation in anterior paracingulate cortex when we mentalize about our opponent. *Source*: Gallagher *et al.*, 2002.

And, we can see a difference in the metabolic activity of the brain that coincides with our adoption of an intentional stance. In Figure 14.22, we can see that the anterior paracingulate cortex (BA 32) is activated – that part of the medial prefrontal cortex implicated in perception of mental states in ourselves and others (Gallagher *et al.*, 2002).

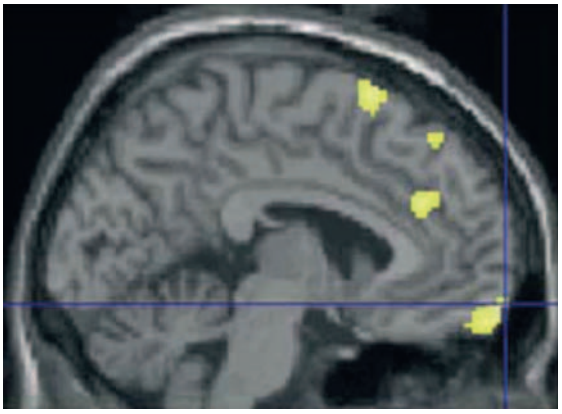


FIGURE 14.23 Adopting the perspective of another to make health care decisions for him or her. Medial PFC activation appears in yellow toward the right. *Source*: Ruby and Decety, 2003.

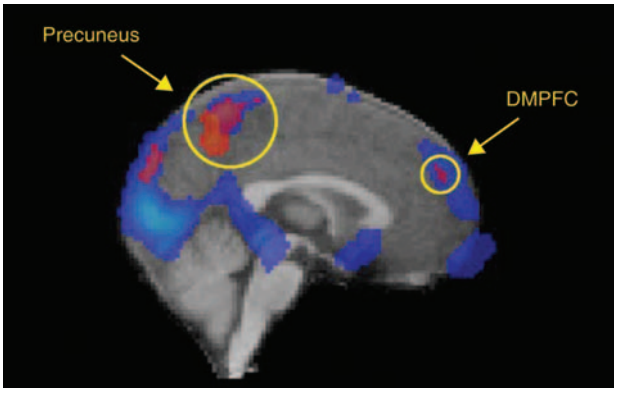


FIGURE 14.24 Thinking about social relationships. Dorsomedial prefrontal cortex and medial parietal cortex system for thinking about social relationships. *Source*: Iacoboni *et al.*, 2004.

We are sometimes asked to make decisions for others, keeping in mind what they would want. In a study where medical students were asked to adopt the perspective of a patient in order to make putative health care decisions for them, PET scans again reveal unique medial frontal activity, in this case, in the medial superior frontal gyrus (Figure 14.23) (Ruby and Decety, 2003).

PET activation appears in the dorsomedial prefrontal cortex (DM-PFC) and medial parietal (precuneus) when study participants watch a film of two people engaged in social interaction (Figure 14.24) (Iacoboni *et al.*, 2004). The same areas are not active when participants watch a single person engaged in solitary activity. The red areas in the figure show activity present during social interaction but not solitary action. The blues areas show activity that was present while participants watched social interaction compared to resting state.

Iacoboni and his colleagues (2004) suggest that:

> The dorsomedial prefrontal cortex and medial parietal cortex system for thinking about social relationships is apparently part of the brain's default state circuitry; it may continuously, often without effort or intention, assess and analyze past, present, or possible future social relationships whenever non-social tasks do not demand full attention (p. 1171).

3.5 Social cognition of others like and unlike us: I-It in the brain?

Of significance for social psychology is the question of how the brain is involved when we perceive others who are like us versus others who are unlike us. When other people are not perceived as belonging to our social in-group, we may feel justified in treating them differently. Among other things, we may deny that they experience higher mental states and feelings. In addition, dissimilar 'others' are more likely to be treated as objects in Buber's (Figure 14.25) sense of I-It (see Box 14.2). It appears that we are close to being able to see brain activity that corresponds to Buber's distinction.

Research by Mitchell *et al*. (2006) reveals distinct activation differences in the medial prefrontal cortex of participants who are asked to make inferences about the preferences of other people who are like them (similar) or not like them (dissimilar) politically. They found that areas in the ventromedial prefrontal cortex (VM-PFC) are active during judgments about similar people, whereas areas in the dorsomedial PFC were active in judgments about dissimilar individuals (Figure 14.26).

Mitchell and his colleagues conclude that, based on their results, we may actively deploy a different set of social cognition strategies in perceiving dissimilar others. Using less of the VM-PFC's perception of dissimilar others implies attributing less feeling and emotion to them. The next section addresses the issue of different strategies for perception of others.

3.5.1 Cognitive versus affective empathy?

Psychologists sometimes make a distinction between cognitive empathy and affective empathy. They point out a difference between theory of mind skills that draw on understanding of others' *beliefs* and empathic skills that help us understand how another person *feels*.

Shamay-Tsoory *et al*. (2005) found differences reflecting this when they tested adults with ventromedial PFC lesions on different kinds of social inference tasks. The researchers asked their participants to answer questions about three kinds of stories, those involving (1) second-order false beliefs, (2) social *faux pas*, and (3) detection of irony. Box 14.3 summarizes the stories and questions that they used. The researchers believed that understanding social *faux pas*

BOX 14.2 In 1923, philosopher Martin Buber wrote about the second person perspective in his classic book *I and Thou*

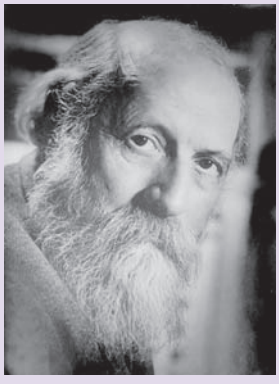


FIGURE 14.25 Martin Buber (1878–1965).

Buber identified two fundamentally different ways of being in relation to other people and objects, I-It and I-thou. I-It involves perceiving others as objects; I-Thou involves an empathic perceiving of others as subjects. Ordinarily we can move easily between these two ways of perceiving others. As we adopt one or the other stance, our own internal states change. Within the past decade, these internal states have been assessed via brain imaging techniques.

Buber wrote:

Primary words are spoken from the being.

If Thou is said, the I of the combination I-Thou is said along with it.

If It is said, the I of the combination I-It is said along with it. . . .

There is no I taken in itself, but only the I of the primary word I-Thou and the I of the primary word I-It. . . .

When Thou is spoken, the speaker has no thing for his object. For where there is a thing there is another thing. Every It is bounded by others; It exists only through being bounded by others. But when Thou is spoken, there is no thing. Thou has no bounds.

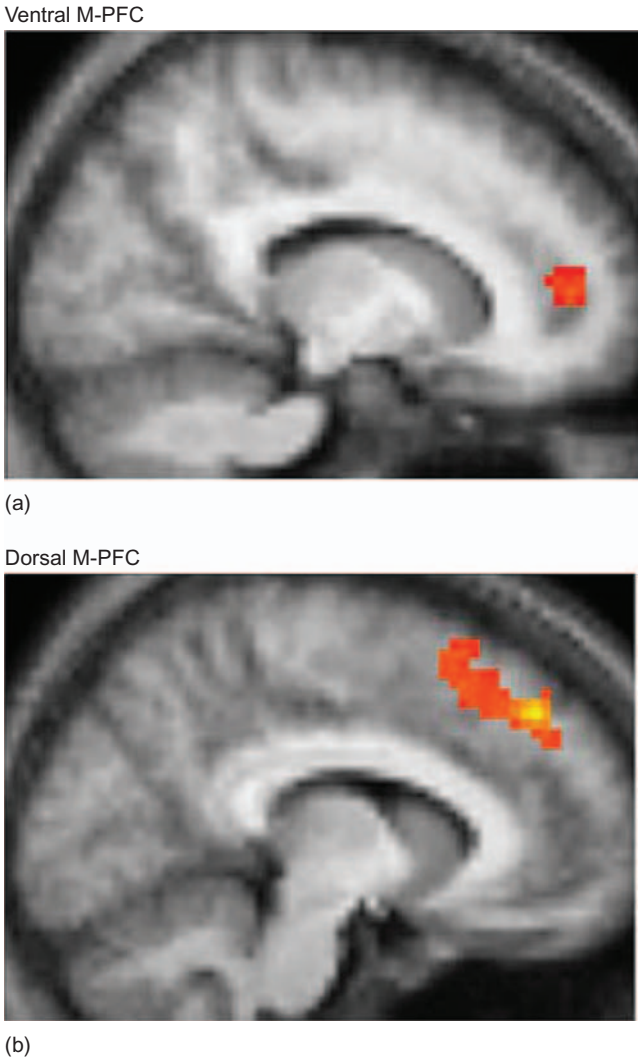


FIGURE 14.26 Understanding similar and dissimilar others. (a) Ventromedial PFC activation in judgments of similar others. (b) Dorsomedial PFC activation in judgments of dissimilar others. *Source*: Mitchell *et al.*, 2006.

and irony involves greater dependence on emotional processing, while second-order false belief tasks rely more heavily on cognitive processing.

Shamay-Tsoory and his colleagues found that patients who had ventromedial prefrontal lesions performed like the healthy control participants and patients with posterior lesions on the second-order false belief task – they all performed at ceiling. However, the VM-PFC patients did very poorly on the irony and social *faux pas* tasks in comparison with other participants. The researchers interpreted these findings to mean that VM-PFC is essential to affective empathy but not to cognitive empathic skills.

BOX 14.3 Stories testing three kinds of social inference

Second-order false belief

Hana and Benny are sitting in the office talking about their meeting with their boss. Benny is putting an open bottle of ink on his desk. As he is doing so, some ink spills, so he leaves the office to look for a towel to clean up the spilled ink. While Benny is out of the office, Hana moves the ink bottle to the cabinet. While Benny is outside the office, he looks back through the keyhole and sees Hana moving the ink bottle. Benny enters the office.

Following the story, four questions were asked:

Belief question: Where will Hana think that Benny thinks the ink bottle is?
Reality question (assessing story comprehension): Where, actually, is the ink bottle?
Memory question: Where did Benny put the ink bottle?
Inference question: Where would there be an ink stain?

Irony

A sarcastic version item: Joe came to work and, instead of beginning to work, he sat down to rest. His boss noticed his behavior and said: 'Joe, don't work too hard!'

A neutral version item: Joe came to work and immediately began to work. His boss noticed his behavior, and said: 'Joe, don't work too hard!'

Following each story, two questions were asked:

Factual question (assessing story comprehension): Did Joe work hard?
Attitude question (assessing comprehension of the true meaning of the speaker): Did the manager believe Joe worked hard?

Recognition of social *faux pas*

Mike, a 9-year-old boy, just started at a new school. He was in one of the cubicles in the bathroom at school. Joe and Peter, two other boys at school, came in and were standing at the sinks talking.

Joe said, 'You know that new guy in the class? His name's Mike. Doesn't he look weird? And he's so short!' Mike came out of the cubicle, and Joe and Peter saw him. Peter said, 'Oh, hi, Mike! Are you going out to play soccer now?'

The participant is then asked the following questions:

Detection of the faux pas *question*:

Did anyone say anything they shouldn't have said?
Who said something they shouldn't have said?
Why shouldn't they have said it?
Why did they say it?

Control question (assessing story comprehension): In the story, where was Mike while Joe and Peter were talking?

Source: (from Shamay-Tsoory *et al.*, 2005)

It appears that empathic abilities follow the general rule that applies to other cognitive skills: facts about the world, beliefs, and sensory representations are processed by the dorsal and lateral cortices. Feelings, emotional values, and social significances depend on ventral and medial cortices that are closely interconnected with the subcortical limbic system.

3.6 Face perception

Perception of the unchanging aspects of the human face occurs in the fusiform face area (FFA), which is part of the inferior temporal lobe (Figure 14.27).

As an example of how the FFA looks in a brain image, we can look at the PET/MRI image from Caldara and colleagues (2006) (Figure 14.28). These researchers compared cortical activation when participants observed objects versus human faces. In the image, we are looking at the bottom of the brain. The temporal lobes take up most of the outside areas of the image. The right and left FFAs are clearly marked in red, showing face receptive areas. Next to the FFAs are other parts of the inferior temporal lobe, the right and left parahippocampal gyri (PHG) that respond to inanimate objects, such as houses or shoes.

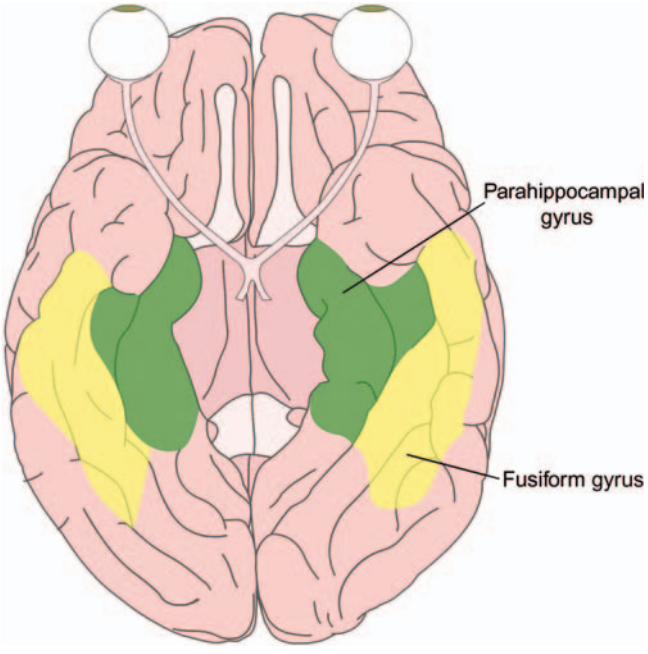


FIGURE 14.27 View from the underside of the theme brain, showing where the fusiform face area (FFA) is located.

Haxby and his colleagues (2002) put the results of numerous studies together to create a model of face perception areas in the brain (Figure 14.29). They proposed a hierarchical system of interconnected brain areas to account for both the changeable and invariant aspects of face perception that have been discussed in this chapter.

In this model, early visual analysis of facial features occurs in the visual cortex, inferior occipital gyrus (IOG). The IOG sends information to the superior temporal sulcus (STS) where changeable aspect of faces, such as eyes, are processed; from there information about eyes is joined with spatial information in the intraparietal sulcus (IPS) to generate gaze direction information. Information from STS can also be sent to the amygdala where social and affective meanings are attached and to the auditory cortex where lip movements are registered. Invariant aspects of faces such as personal identity are processed in the lateral fusiform gyrus (the FFA) that is interconnected with the temporal lobe where specific information about name and biographical data are retrieved.

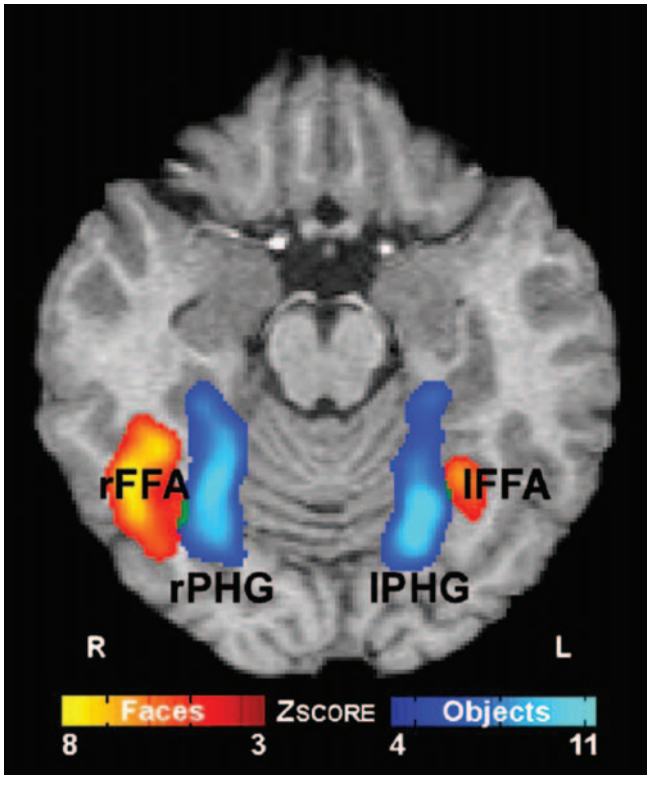


FIGURE 14.28 A view of the underside of the brain with fusiform face areas (FFA) shown in red and parahippocampal gyri (PHG) shown in blue. *Source*: Caldara *et al.*, 2006.

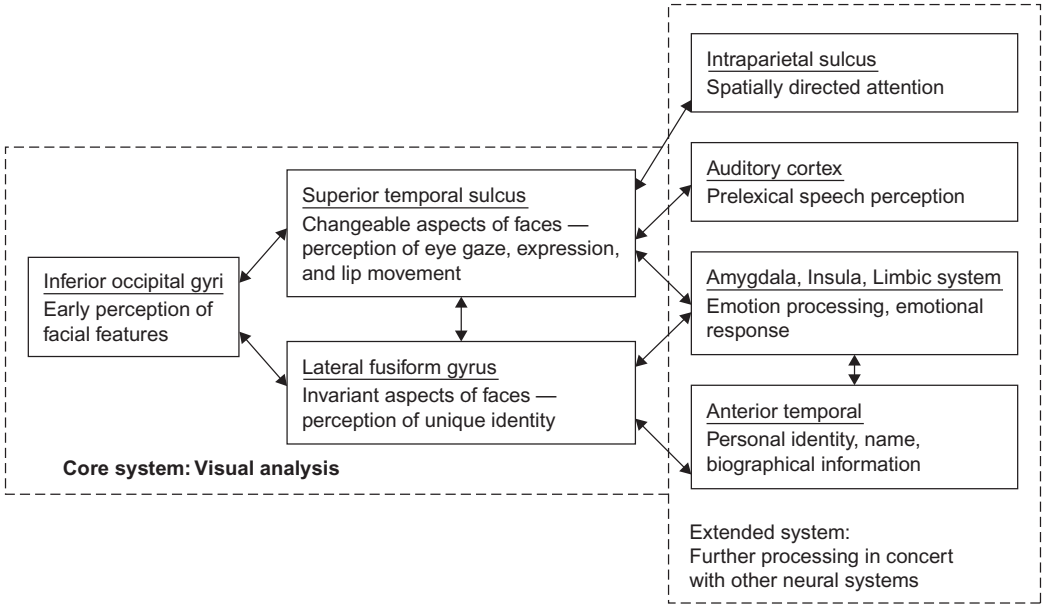


FIGURE 14.29 Model of facial perception developed by Haxby and colleagues. The left side of the model shows early visual regions for face perception, the center shows brain regions for changing and non-changing features in faces, and the right side shows further processing of facial features. *Source*: Haxby *et al.*, 2002.

4.0 SUMMARY

Social cognition abilities in human beings are complex and multifaceted. They are supported by multiple systems of interconnected cortical and subcortical areas. During evolution, the simpler valuation and behavioral system of the limbic brain was overlaid by the growing cerebral cortices that make complex cognition possible. It is very likely that our large and complex cerebral cortices evolved in part due to selective pressures brought to bear by the increasing complexity of human society and the demands of social cognition. Increasing social and cognitive complexity in the environment go hand in hand with increasing complexity in the correlated brain systems.

5.0 CHAPTER REVIEW

5.1 Study questions

1. Briefly describe what is meant by a theory of mind.
2. According to Frith, what is mentalizing?
3. Why are shared attention mechanisms important for human development? When do they develop?
4. How do mirror neuron systems differ from other neuron systems? What is their role in social cognition?
5. What role does context play in understanding intention?
6. Why is perspective taking a key social skill?

5.2 Drawing exercises

1. Label the key brain regions (shown in shades of red and pink in Figure 14.30) of the theorized frontal mirror neuron system.

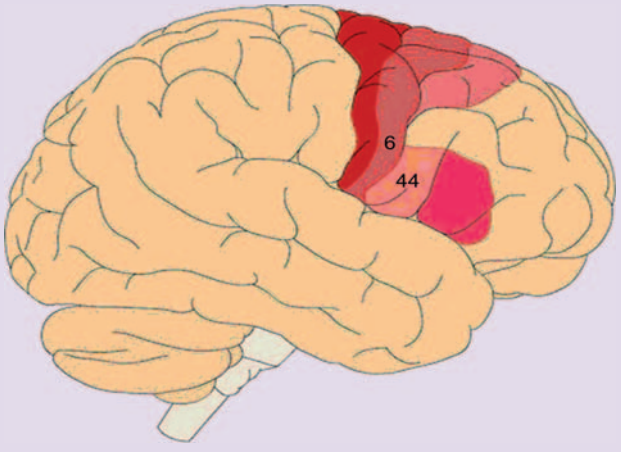
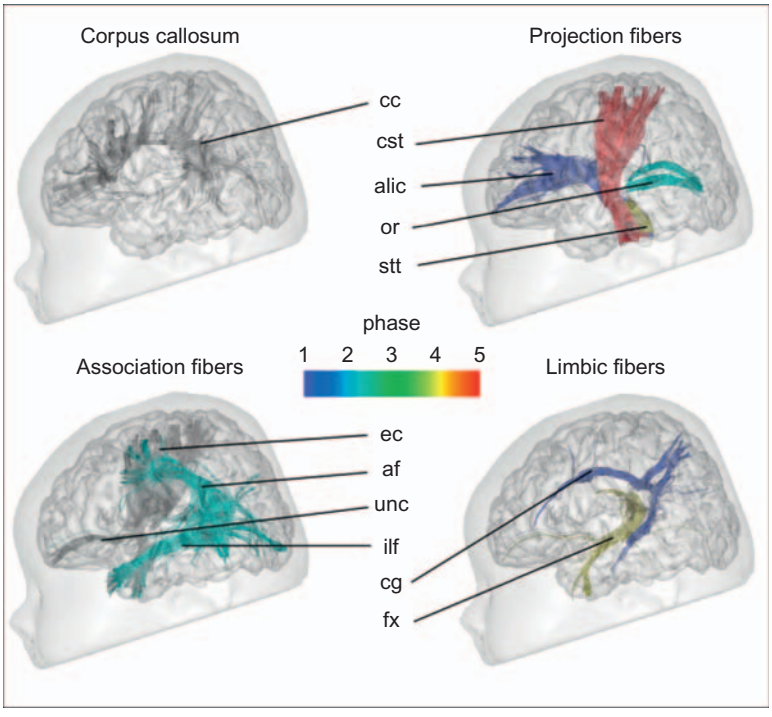


FIGURE 14.30

Life is a flame that is always burning itself out, but it catches fire again every time a child is born.

George Bernard Shaw



The mature adult brain contains neural 'highways' that are well established and course throughout the brain. Until recently, little was known about the development of these neural highways in living infants. Using new diffusion tensor imaging techniques, the maturation of fiber bundles is studied in 1–4 month old infants. The color coding (from blue to red) shows the maturational phase of the fiber bundles. *Source*: Debois *et al*., 2009.

CHAPTER

15

Development

OUTLINE

1.0 INTRODUCTION

In this chapter, we provide an overview of how humans grow and develop across multiple stages of life: from prenatal to infancy, from child to adolescent. Much of our focus will be on early stages of brain and cognitive development because the first years of human life represent a dramatic explosion of neurodevelopmental change as babies learn about their world. We will explore the roles of nature and nurture in the development of the brain and mind, discovering the intricacies of the complex interactions between genetics and experience.

The field of developmental cognitive neuroscience – i.e. the investigation of the maturing brain and its correspondence to human cognition – is a relatively young one. The advent of new non-invasive ways to measure brain function in infants and children has literally revolutionized the study of what infants and young children understand about the world surrounding them. A central focus of the study of the development

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

of the brain and its relation to behavior relies on the combination of multiple techniques and experimental approaches in order to elucidate the complexities of the mind-brain.

In this chapter, we will briefly discuss the emerging techniques for investigating infant and child development. Next, we will trace the anatomical development of the brain from prenatal to postnatal stages of life. We then focus on brain and cognitive development in the first year of life: an explosive time of large-scale changes both in brain and in cognition. Next, we track mind-brain development through childhood and adolescence. We end the chapter looking at the long-term effects of early perinatal brain damage with a discussion of brain plasticity in childhood. Throughout the chapter, we highlight recent empirical investigations of the development of the brain and its correspondence to cognition; however, we add a caveat as this field of study is relatively new and we are only beginning to understand the relationship between the brain and human behavior.

1.1 New techniques for investigating the developing brain

The emergence of new ways to investigate the human brain has been discussed in Chapter 4. Two techniques that have been employed in studies of infants and young children are electroencephalography/event-related potentials (EEG/ERPs) and functional magnetic resonance imaging (fMRI) (Figure 15.1). While these techniques have revolutionized the young field of cognitive neuroscience, nowhere is the effect felt as strongly as in the study of the unfolding of human brain development and its correspondence to behavior. Studies of adult behavior and brain function have informed us about how the

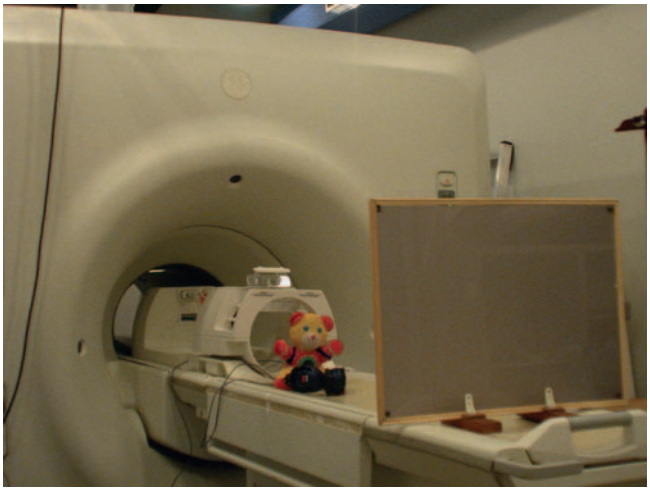


FIGURE 15.1 Techniques for studying brain function in infants and children: top panel shows an EEG electrode array; bottom left panel shows an MRI set up for scanning infants and children; right panel shows a specialized infant seat for us in MRI scanning. *Source*: Ghislaine Dehaene-Lambertz, with permission.

typically developing brain functions across domains such as language, emotion, and memory. They also inform us about the effects of brain damage or disease. However, the pattern of deficit found in adults following brain damage differs sharply from the effects when brain damage occurs early in life. Therefore, the advent of neuroimaging techniques allows us to understand the brain regions and cognitive capabilities across cognitive domains while it is unfolding in development.

New and sophisticated methods to investigate anatomical developmental changes throughout life have also increased our ability to understand the complex patterns of brain development (Figure 15.2). These methods allow us to track the development of gray matter across brain regions as well as to assess connectivity patterns across and between the cerebral hemispheres.

1.2 The mystery of the developing brain: old questions and new

In this chapter, we address some brain questions that have been asked for many years. A central question in human development is the trading roles of nature and nurture. A related issue is to what extent the brain is flexible in adapting to new situations in its environment and to recover from damage. Some new questions can be posed that we were previously unable to address due to the limitation of our experimental approaches or techniques, such as what does a baby know before birth? What are the long-standing effects of very early brain damage? How do dynamic processes in brain development differ across brain regions and hemispheres? We will discuss advances in our knowledge about the developmental pathways of three main areas of cognition that have been a focus in the field: language, executive function, and social cognition.

2.0 PRENATAL DEVELOPMENT: FROM BLASTOCYST TO BABY

Much of this chapter will be devoted to a discussion of brain development and its correspondence to cognition during infancy and childhood. Before we begin that

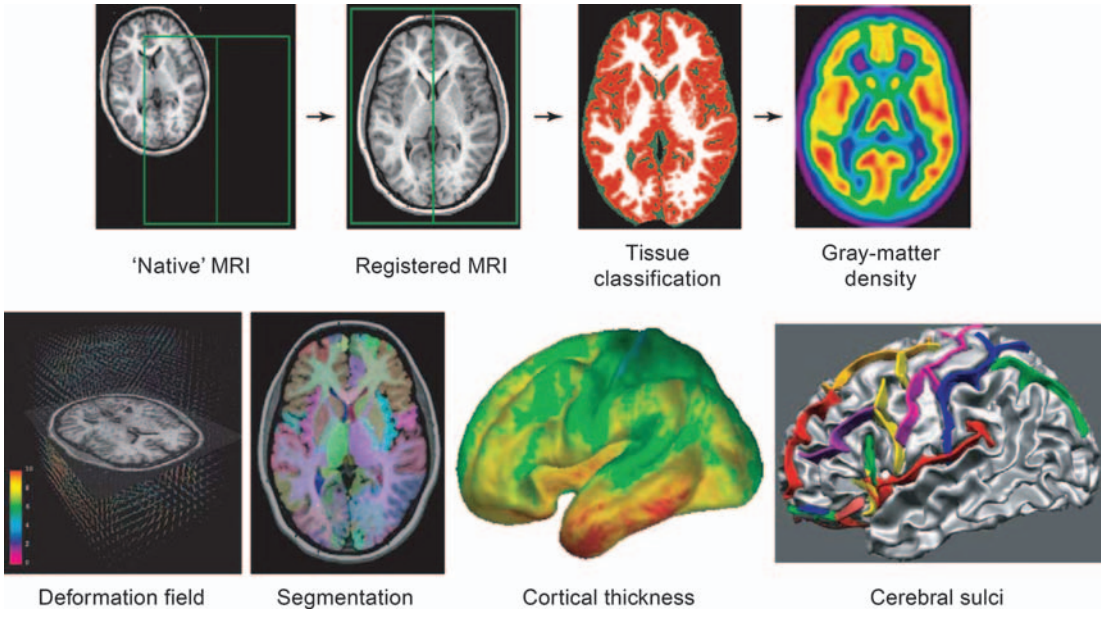


FIGURE 15.2 Image processing pipeline. *Top row*: a typical image processing pipeline begins with a transformation of a magnetic resonance (MR) image from the acquisition ('native') to standardized stereotaxic space; this process generates an image that is 'registered' with the template brain. The next step involves voxel-wise classification of brain tissue into three main classes: gray matter (in red), white matter (in white), and cerebrospinal fluid (in green). Each of these binary images (0, tissue absent; 1, tissue present) is then filtered (or smoothed) to generate 'density' images; the image of gray matter (GM) density shown here indicates, at each voxel, the local concentration of GM on a continuous scale from 0 to 1 (the 'hotter' the color, from blue to red, the higher the value of GM density). *Bottom row*: non-linear registration of the sample image to the template brain allows one to characterize local shape differences; the deformation field quantifies such sample-template differences throughout the brain. By combining non-linear registration with tissue classification, one can segment automatically various brain structures, such as the frontal lobe or the amygdala. Other techniques produce maps of cortical thickness or identify sulci in the subject's cerebral cortex. *Source*: Paus, 2005.

discussion, we provide a brief description of the processes that occur before birth, during prenatal development. While little is known about the sensory, perceptual, or cognitive processes of a fetus *in utero*, recent investigations have focused on what a baby experiences before birth. These pre-birth experiences can be critical for later development. And whether they are positive – hearing a mother's voice or her heartbeat – or negative – experiencing the effects of maternal alcohol abuse – these prenatal experiences can have long-standing effects on later cognitive and social development. Let's begin our prenatal section with a discussion of gene expression and the role of the environment.

2.1 Epigenesis

A central debate in the field of human development is the influence of nature versus nurture. Does our genetic makeup predetermine who we will become? Or does our experience shape who we are? Clearly, both genes and the environment have an impact on the developing human. Does gene expression unfold, followed by the development of brain structures and functions that later are affected by experience? Or does experience – the local environment, whether within a cell, a system, or the brain *in toto* – have an affect on gene expression? The interplay between genes and the environment is a complex one, with these interactive processes occurring long before birth. Here, we begin the topic of the cognitive neuroscience of human development with a discussion of the nature of epigenesis.

Epigenesis, the unfolding of genetic information within a specific context, is key to modern ideas about development. Different viewpoints on epigenesis underlie different perspectives on developmental cognitive neuroscience. Gottlieb and Halpern (2002) have drawn a useful distinction between 'predetermined epigenesis' and 'probabilistic epigenesis'. *Predetermined epigenesis* assumes that there is a unidirectional causal pathway from genes to brain anatomy to changes in brain and cognitive function. A hypothetical example of this would be if the endogenous expression of a gene in the brain generated more of a certain neurochemical. Higher levels of this neurochemical might make a particular neural circuit active in the brain, and this additional neural activity allows for more complex computations than were previously possible. This increased cognitive ability will be evident in behavior as the child being able to pass a task that he or she failed at young ages. In contrast, *probabilistic epigenesis* views the interactions between genes, structural brain changes, and function as bidirectional (Figure 15.3).

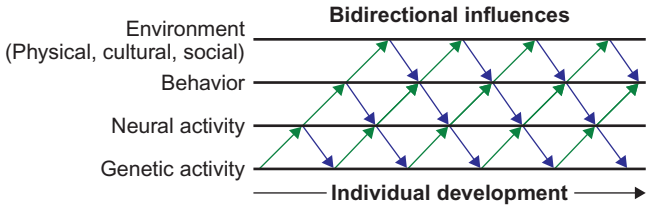


FIGURE 15.3 A systems view of psychobiological development. *Source*: Adapted from Gottlieb and Halpern, 2002.

Bidirectional interactions mean that not only can genes trigger a behavioral change, but also that sensory input to the child can change patterns of gene expression. For example, we will hear later that newborn infants have primitive brain circuits that bias them to look toward the faces of other humans (Johnson, 1991). This early attention to faces results in some of the neural circuits involved in the visual pathways of the baby becoming shaped or tuned to process faces. The neuroanatomical changes that underlie this shaping process are due to differential gene expression.

2.2 The anatomy of brain development

Much of early brain development occurs in the first weeks following fertilization and we will focus on those processes here. Shortly after conception, a fertilized cell undergoes a rapid process of cell division, resulting in a cluster of proliferating cells (called the *blastocyst*) that resembles a tiny bunch of grapes (Figure 15.4). After a few days, the blastocyst differentiates into a three-layered structure (the embryonic disk). Each of these layers will subsequently differentiate into a major organic system, with the *endoderm* (inner layer) becoming internal organs (digestive, respiratory, etc.), the *mesoderm* (middle layer) becoming skeletal and muscular structures, and the *ectoderm* (outer layer) developing into the skin surface and the nervous system (including the perceptual organs).

The nervous system itself begins with a process known as *neurulation*. A portion of the ectoderm begins to fold in on itself to form a hollow cylinder called the *neural tube* (Figure 15.5).

The neural tube differentiates along three dimensions: length, circumference, and radius. The length dimension differentiates into components of the central nervous system, with the forebrain and midbrain arising at one end and the spinal cord at the other (Figure 15.6). The end of the tube that will become the spinal cord differentiates into a series of repeated units or segments, while the other end of the neural

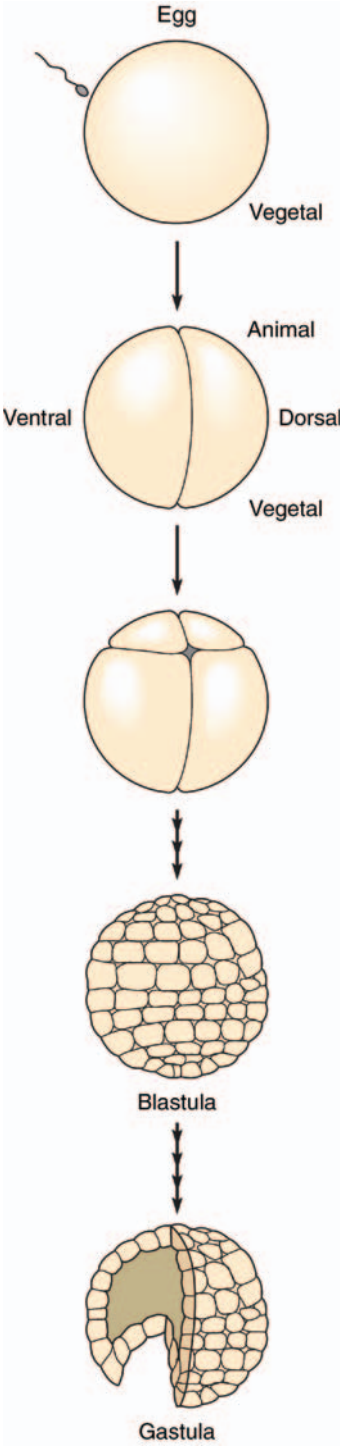


FIGURE 15.4 Blastocyst development. The early processes of animal development follow a conserved pattern; after fertilization, a series of cleavage divisions divide the egg into a multicellular blastula. The animal and vegetal poles represent an initial asymmetry in the oocyte, and the second axis, dorsal-ventral in this example, is established after fertilization. The process of gastrulation brings some of the cells from the surface of the embryo to the inside and generates the three-layered structure common to most multicellular animals. *Source*: Sanes *et al.*, 2006.

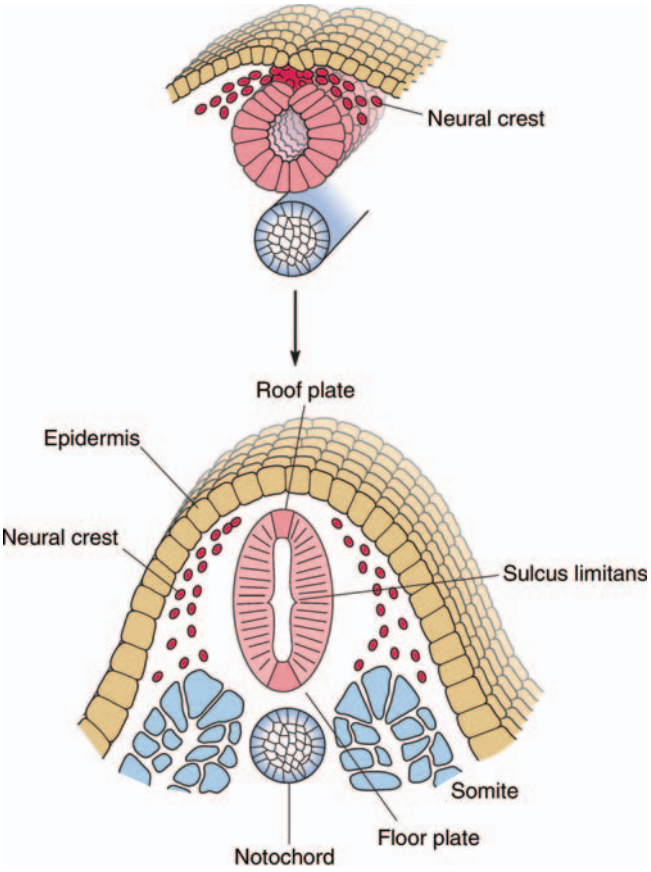


FIGURE 15.5 The neural tube. The overall organization of the neural tube emerges soon after closure. The most ventral part of the neural tube becomes flattened into a distinct 'floor plate'. The most dorsal aspect of the neural tube develops into a tissue known as the roof plate. A distinct fissure, the *sulcus limitans*, forms between the dorsal and ventral parts of the neural tube along most of its length. *Source*: Sanes *et al.*, 2006.

tube organizes and forms a series of bulges and convolutions. Five weeks after conception these bulges become protoforms for parts of the brain. One bulge gives rise to the cortex, a second becomes the thalamus and hypothalamus, a third turns into the midbrain, and others form the cerebellum and medulla.

The distinction between sensory and motor systems develops along the axis tangential to the surface of the neural tube with the dorsal (top-side) becoming mainly sensory cortex, and the ventral (bottom-side) developing into motor cortex. The various association cortices and 'higher' sensory and motor cortices tend to arise from the tissue between.

The radial dimension of the tube differentiates into some of the layering patterns in the adult brain. Across the radial dimension of the neural tube the

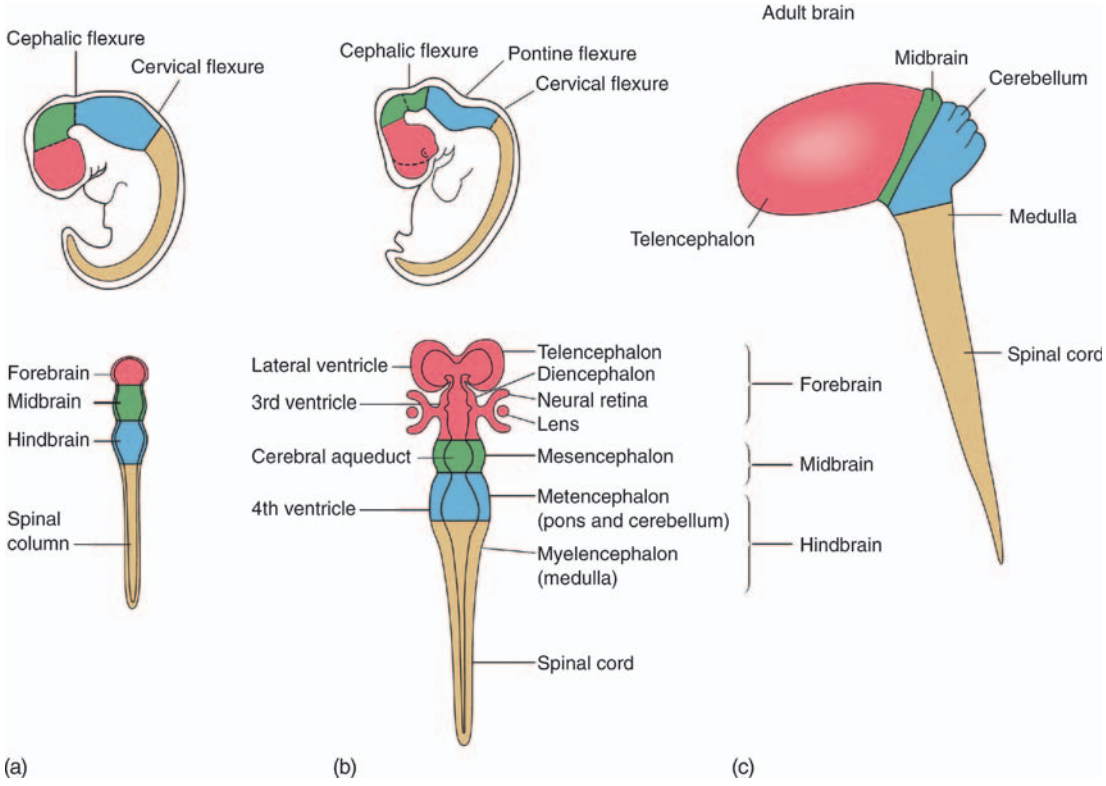


FIGURE 15.6 The vertebrate brain and spinal cord develop from the neural tube. Shown here as lateral views (upper) and dorsal views (lower) of human embryos at successively older stages of embryonic development (a,b,c). The primary three divisions of the brain (a) occur as three brain vesicles or swellings of the neural tube, known as the forebrain (prosencephalon), midbrain (mesencephalon), and hindbrain (rhombencephalon). The next stage of brain development (b) results in further subdivisions, with the forebrain vesicle becoming subdivided into the paired telencephalic vesicles and the diencephalon, and the rhombencephalon becoming subdivided into the metencephalon and the myelencephalon. These basic brain divisions can be related to the overall anatomical organization of the mature brain (c). *Source*: Sanes *et al.*, 2006.

bulges grow larger and become more distinctive. Within these bulges cells *proliferate* (are born), *migrate* (travel), and *differentiate* into particular types. The vast majority of the cells that will compose the brain are born in *proliferative zones* (Figure 15.7). These zones are close to the hollow center portion of the tube (that itself later becomes the ventricles of the brain). One of these proliferation sites, the *ventricular zone*, may be phylogenetically older (Nowakowski, 1987). Another, the *subventricular zone*, only contributes significantly to phylogenetically recent brain structures such as the neocortex (i.e. 'new' cortex since it's only found in mammals). These two zones yield separate glial (support and supply cells) and neuron cell lines and give rise to different forms of migration.

Neurons and *glial cells* are produced by the division of cells within the proliferative zone to produce *clones* (a clone is a group of cells which are produced by division of a single precursor cell – such a precursor cell is said to give rise to a lineage) (Figure 15.8). *Neuroblasts* produce neurons, with each giving birth to a definite and limited number of neurons. In some cases neuroblasts give rise to particular types of neurons. For example, less than a dozen proliferating cells produce all the Purkinje cells of the cerebellar cortex, with each producing about 10 000 cells (Nowakowski, 1987).

2.3 Neural migration

After young neurons are born, they have to *migrate* from the proliferative zone to the particular region where they will be employed in the mature brain. The most common type of migration involves *passive cell displacement*. In this case young cells are simply pushed farther away from the proliferative zone by more recently born cells. This gives rise to an outside-to-inside pattern, resulting in the oldest cells ending up toward the surface of the brain, while the youngest cells are toward the inside. This type of migration gives rise to brain structures such as the thalamus and many regions of the brainstem.

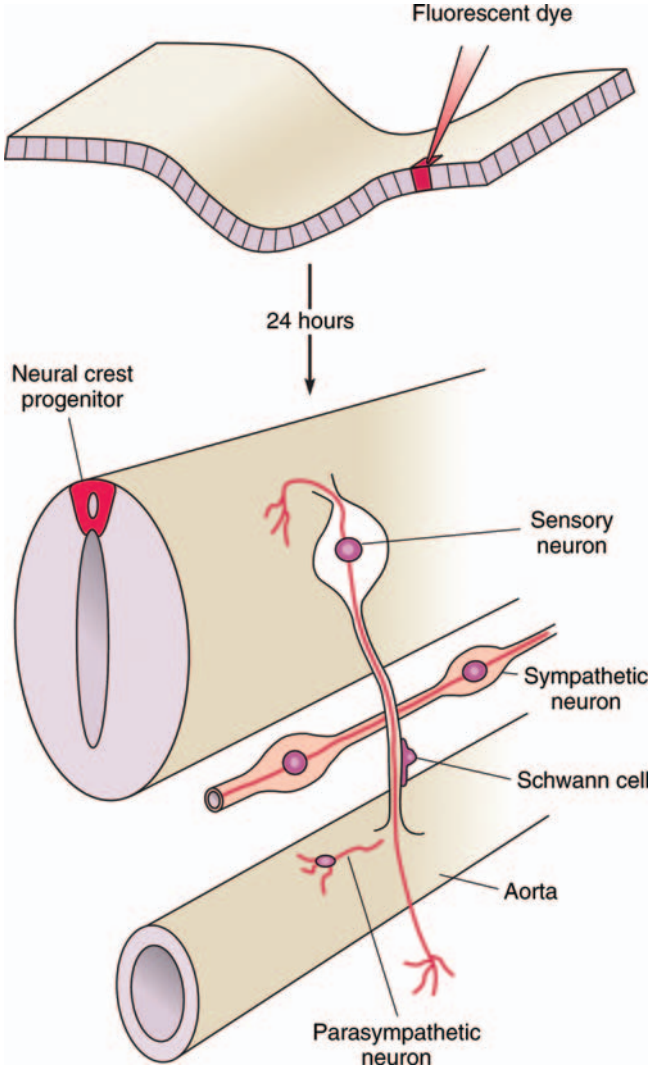


FIGURE 15.7 Fates and migration of neural crest cells. A single progenitor cell is injected with a lineage tracer, and its progeny are followed as they migrate out of the neural tube. Some may become sensory neurons, while others become Schwann cells or neurons of the autonomic nervous system. Environments these cells pass through on their migration routes influence their fate choice. *Source*: After Bronner-Fraser and Fraser, 1991; Sanes *et al.*, 2006.

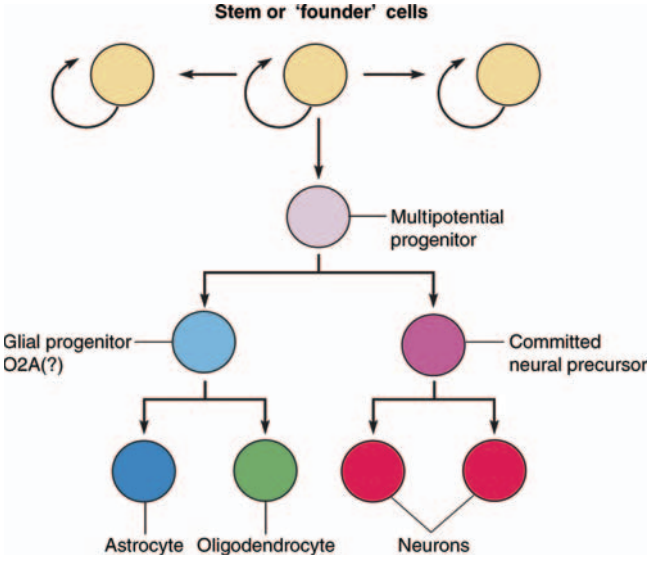


FIGURE 15.8 Basic lineage relationships among the cell types of the central nervous system of vertebrates. Through a variety of cell cultures and *in vivo* studies, the relationships among the various cell classes within the nervous system have been established. The early cells of the neural tube have the potential to generate an enormous number of progeny and, as a result, are sometimes called founder cells or stem cells, which undergo symmetric cell divisions to produce additional founder cells as well as progenitor cells. (The term stem cells is also used to describe the persistent progenitors found in adult animals.) It is thought that the early founder cells also generate progenitor cells that are capable of a more limited number of cell divisions, and this is the reason that clones of progenitor cells labeled late in embryogenesis have fewer progeny. Nevertheless, the late progenitor cells are capable of generating both neurons and all macroglia, the oligodendrocytes and the astrocytes. Although *in vitro* studies of certain regions of the nervous system, particularly the optic nerve, have shown that the lineages of astrocytes and oligodendrocytes share a common progenitor, known as the O2A glial progenitor, in the spinal cord, motoneurons and oligodendrocytes share a common progenitor. Thus, the lineage relationships shown may vary depending on the region of the CNS. *Source*: Sanes *et al.*, 2006.

The second form of migration is more active and involves the young cell moving past previously generated cells to create an '*inside-out' pattern* (Figure 15.9). This pattern is found in the cerebral cortex and in some subcortical areas that have a laminar structure (divided into parallel layers) (Figure 15.10).

The best studied example of active migration comes from the prenatal development of cerebral cortex and the *radial unit model* proposed by Pasko Rakic (1988). As mentioned earlier, most cortical neurons in humans are generated outside the cortex itself in a region just underneath what becomes the cortex, the 'proliferative zone'. Recall that the cerebral cortex is much more extensive in humans than in most other species. This means that these cells must migrate to take up their final locations within the cortex. Rakic proposed a '*radial unit model*' of neocortical differentiation that gives an account of how *both* the regional and the layered structure of the mammalian cerebral cortex arise (Rakic, 1988). According to his model, the laminar organization of the cerebral cortex is determined by the fact that each relevant proliferative unit gives rise to about one hundred neurons. The progeny from each of these proliferative units all migrate up the same radial glial fiber, with the latest to be born travelling past their older relatives. A radial glial fiber is a long process that stretches from top to bottom of the cortex and originates from a glial cell.

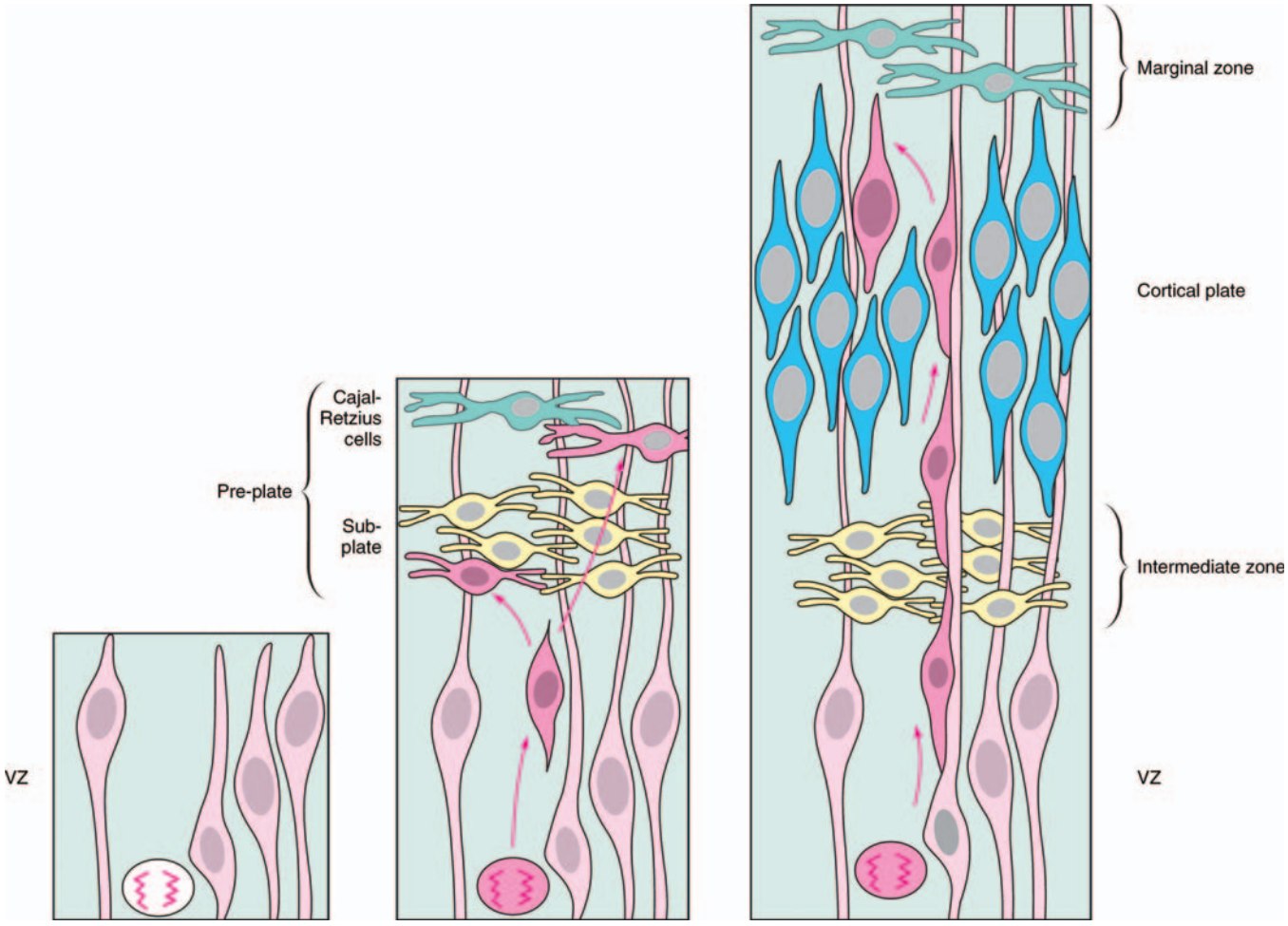


FIGURE 15.9 Histogenesis in the cerebral cortex proceeds through three stages. In the first stage of histogenesis, the wall of the cerebral cortex is made up of the progenitor cells, which occupy the ventricular zone (VZ). In the next stage of development, the first neurons exit the cell cycle (red) and accumulate in the preplate, adjacent to the pial surface. The neurons of the preplate can be divided into the more superficial Cajal-Retzius cells and the subplate cells. In the next stage of cortical histogenesis, newly generated neurons (red) migrate along radial glial fibers to form a layer between the Cajal-Retzius cells and the subplate. This layer is called the cortical plate, and the majority of the neurons in the cerebral cortex accumulate in this layer. *Source*: Sanes *et al.*, 2006.

Radial glial fibers effectively act like a climbing rope to ensure that neurons produced by one proliferative unit all contribute to one radial column within the cortex (Figure 15.11).

There are some interesting consequences of the radial unit model for species differences in the cerebral cortex. Rakic (1988) points out that greater cell division at the proliferative unit formation stage would increase the number of cortical columns and hence the total area of cortex that results. In contrast, an additional single round of division at a later stage, from the proliferative zone, would only increase the size of a column by one cell (about 1 percent). This corresponds well with the fact that there is very little variation between mammalian species in the general layered structure of the cortex, while the total surface area of the cortex can vary by a factor of 100 or more between different species of mammal. It seems likely, therefore, that species differences originate (at least in part) in the number of 'rounds' of cell division that are allowed to take place within and across regions of the proliferative zone.

Thus, in the early weeks of gestation, the embryo undergoes complex processes that form the basis for the central nervous system. It is important to note that prenatal brain development is not a passive process involving the unfolding of genetic instructions. Rather, from an early stage *interactions* between cells are critical, including the transmission of electrical signals between neurons. In one example, patterns of spontaneous firing of cells in the eyes (before they have

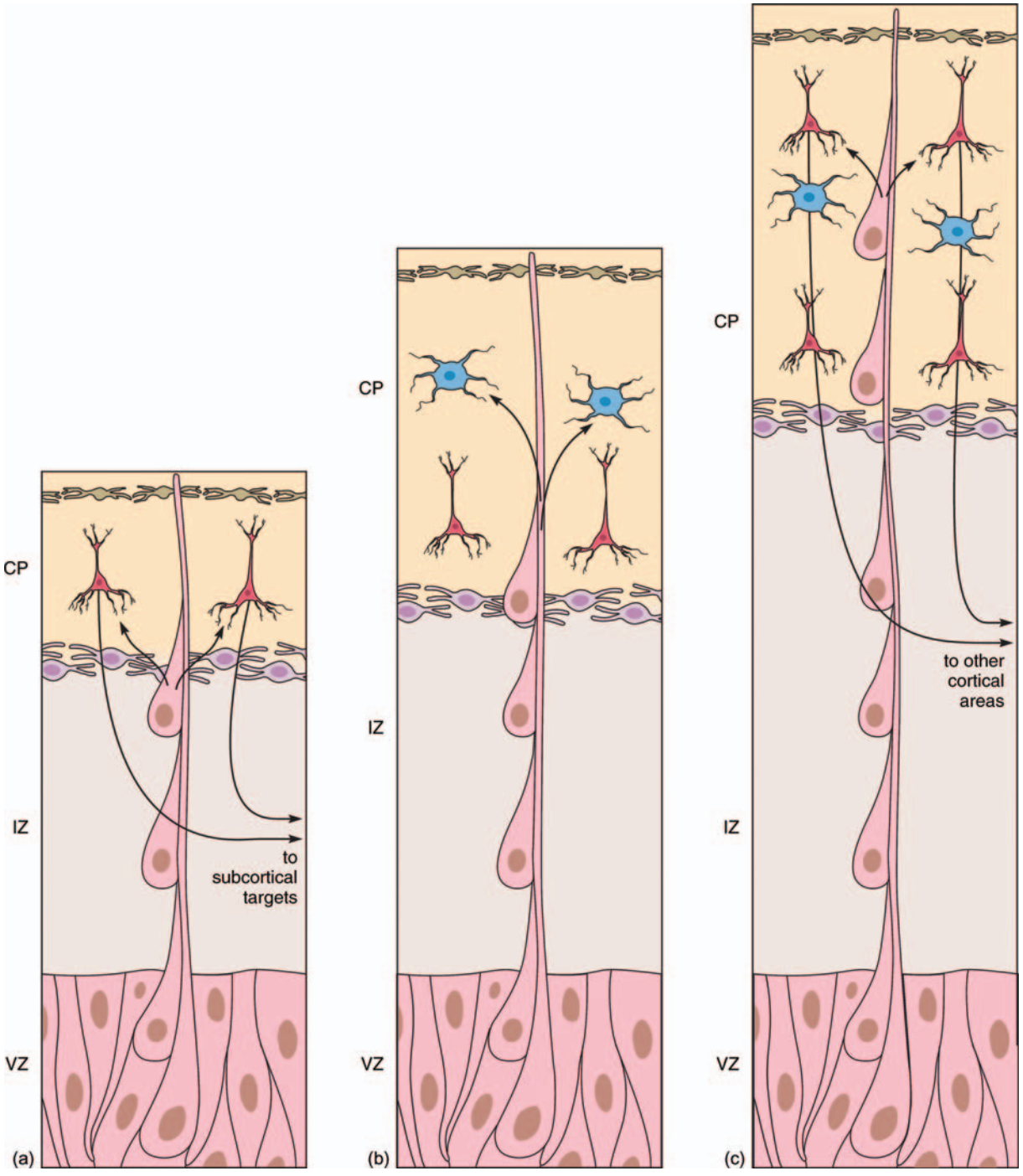


FIGURE 15.10 Histogenesis of pyramidal neurons of the deep layers, V and VI. (a) After the birth and migration of the Cajal-Retzius cells and the subplate cells, the next neurons to be generated in the cortex are the pyramidal neurons of the deep layers, V and VI, whose axons project to subcortical targets. (b) The next neurons to be born are the local interneurons in layer IV of the cortex. (c) Finally, the pyramidal cells of the upper layers, II and III, are generated. They send axons to other cortical areas. *Source*: Sanes *et al.*, 2006.

opened in development) transmit signals that appear to specify the layered structure of the visual thalamus, the lateral geniculate nucleus (LGN) (see Shatz, 2002; O'Leary and Nakagawa, 2002). Thus, waves of firing intrinsic to the developing organism may play an important role in specifying aspects of brain structure long before sensory inputs from the external world have any effect.

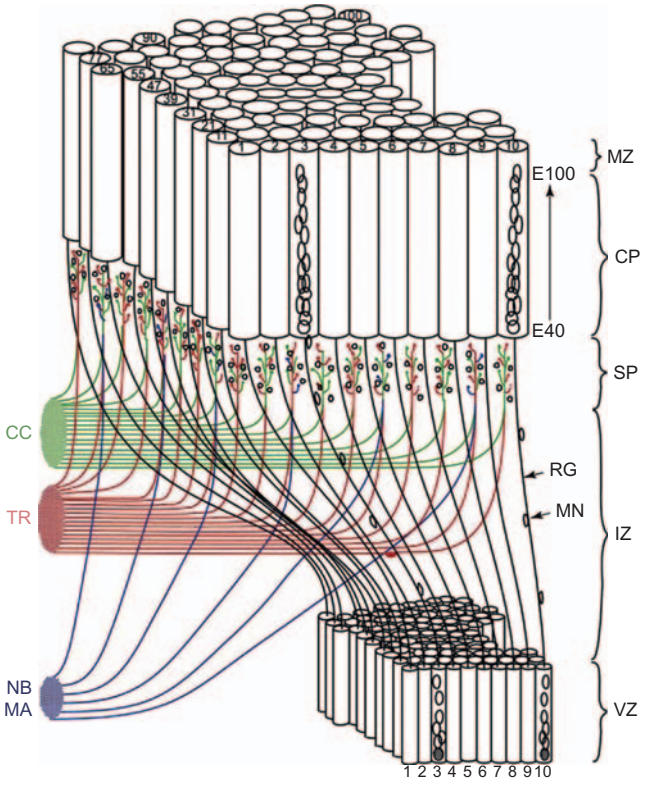


FIGURE 15.11 The radial unit model of Rakic (1988). Radial glial fibers span from the ventricular zone (VZ) to the cortical plate (CP) via a number of regions: the intermediate zone (IZ) and the subplate zone (SP). RG indicates a radial glial fiber, and MN a migrating neuron. Each MN traverses the IZ and SP zones that contain waiting terminals from the thalamic radiation (TR) and cortico-cortico afferents (CC). As described in the text, after entering the cortical plate, the neurons migrate past their predecessors to the marginal zone (MZ). *Source*: Rakic *et al.*, 2009.

2.4 Nature and nurture revisited

As we mentioned at the beginning of this section, the role of the prenatal environment in the unfolding of genetic instructions and brain development can have long-lasting effects, both good and bad. The developing infant is susceptible to events occurring within this environment. One such event is the incursion of a *teratogen*. A teratogen is defined as any environmental agent that causes damage during the prenatal period. Examples of teratogens are prescription and even non-prescription drugs, caffeine found in coffee and soft drinks, illegal drugs such as cocaine and heroin, tobacco and marijuana products, and alcohol. The effects of the teratogen(s) can be complex depending on the dosage level, the time it occurs during prenatal development, and the genetic makeup of the mother, since some individuals are more susceptible than others. Prenatal counseling for mothers-to-be providing education regarding potential sources of teratogens has helped to reduce the occurrences of brain damage due to teratogens.

The prenatal brain is particularly susceptible to the effects of alcohol. Alcohol abuse by the mother during pregnancy results in long-term deficits in cognition, language, and social development called *fetal alcohol syndrome* (FAS) (Jones and Smith, 1973; Jones, 1975). A recent brain mapping study of children, teenagers, and young adults with severe FAS showed gray matter density differences in FAS individuals as compared to age- and gender-matched controls. Specific findings were reduced gray matter density in frontal and parietal areas and increased density in temporal and inferior parietal lobe regions (Figure 15.12). As we will see in later sections of this chapter, these brain areas mature throughout childhood and into late adolescence; therefore these gray matter density differences in FAS individuals indicate that prenatal exposure to alcohol has a resounding and long-lasting impact on brain development and cognitive development throughout the lifespan.

Longitudinal studies assessing the long-term effects of smoking cigarettes or marijuana during pregnancy have provided new evidence about their impact on a child's cognitive development. Fried and colleagues (Fried *et al.*, 2003) have followed a cohort of children in Canada from birth through young adulthood. Using neuropsychological test batteries to assess cognitive functions like verbal intelligence, visuo spatial processing, language abilities, attentional function, Fried and colleagues found that there are early-occurring (by age 3) and long-lasting cognitive impairments caused by the mother smoking either tobacco or marijuana during pregnancy. The specific effects of prenatal exposure to cigarette smoke differ sharply from exposure to marijuana, although both cause harm. Exposure to cigarette smoke resulted in lower general intelligence in the children coupled with deficits in auditory function and verbal working memory that continued from early childhood (age 3) through adolescence (age 16) (Fried *et al.*, 2003). Exposure to marijuana smoke resulted in no general intelligence deficit; however, executive functions, such as attention and working memory, were impaired in these children and, in particular, visual processes such as visual integration, analysis, and reasoning. Again, these impairments were observed early (age 3) and continued through the teenage years.

The cognitive impairments reflected by the neuropsychological test batteries implicated specific brain regions for further study of the effects of prenatal exposure to cigarette and marijuana smoke. Visuospatial

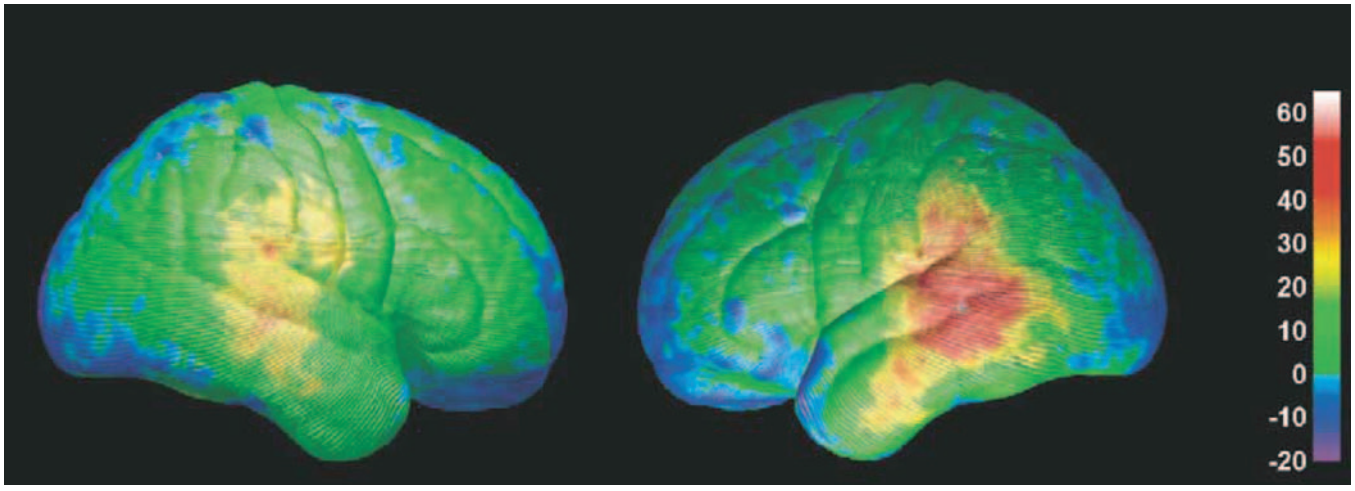


FIGURE 15.12 Differences in gray matter density between children with fetal alcohol syndrome (FAS) and typically developing controls. Warm (red, yellow) colors represent positive differences, indicating an increase in gray matter density (and thus a decrease in normal 'pruning') in those regions as compared to controls. Note that the children with FAS have much increased densities in temporal lobe regions, particularly in the left hemisphere. (Adapted, with permission, from Sowell *et al.*, 2002.) *Source*: Toga *et al.*, 2006.

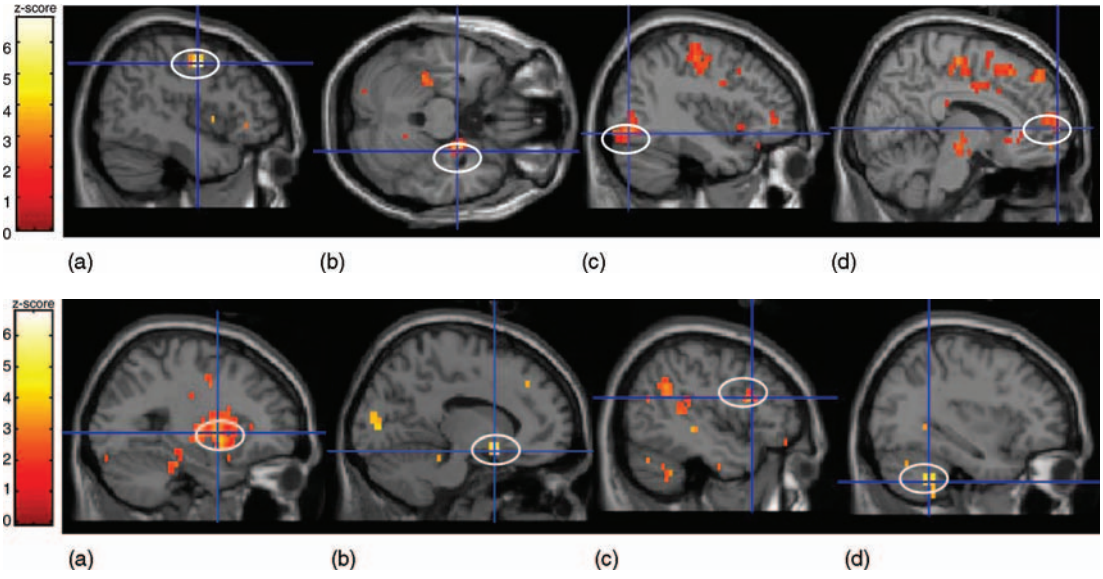


FIGURE 15.13 Effects of prenatal use of marijuana smoke on young adults (18–22 years) measured using fMRI. Frontal lobe circuits engaged in a task tapping visuospatial working memory systems, with reduced right hemisphere activity (upper panel) and increased left hemisphere activity (lower panel) as compared to an age-matched control group. *Source*: Smith *et al.*, 2006.

integrative processes tap frontal lobe regions in adults (see Chapter 6). Fried and colleagues (Smith *et al.*, 2006) continued their investigation into the long-term effects of prenatal exposure to marijuana using a neuroimaging technique, fMRI, with a sample of young adults (18–22 years) from the Canadian cohort with prenatal exposure to marijuana smoke. Results of the study revealed a differing pattern of neural activity in frontal lobe regions that are engaged in a visuospatial task. Specific findings were reduced activity in right hemisphere regions (Figure 15.13, upper panel) and increased activity in left hemisphere regions (Figure 15.13, lower panel). The authors interpreted these findings as indicating that right hemisphere neural circuitry engaged in tasks that tap visuospatial short-term memory are less active in children with prenatal marijuana

smoke exposure. While it is difficult to know at this stage of the research just why left hemisphere activity was increased, it could be that left hemisphere regions were recruited as a compensatory mechanism due to the decreased neural activation in the right hemisphere. More research is clearly needed in order fully to understand the effects of prenatal cigarette and marijuana smoke exposure. However, the work of Fried and colleagues provide compelling evidence that the damage appears early in a child's cognitive development and is very long lasting. The clear message from these studies is that early insult caused by a teratogen, such as cigarette or marijuana smoke, can produce lifelong cognitive impairment and may correspond to differing patterns in cortical development.

2.5 Prenatal hearing experience: voice and music perception before birth

What do babies know before they are born? Is it important for a mother-to-be to talk to her unborn baby? Read to her baby? Sing to her baby? Is there an impact on later language, music, and cognitive function? In other words, what are the perceptual abilities of an unborn child and how do they relate to later cognitive development? This question has intrigued developmental psychologists for at least a hundred years (see Kisilevsky and Low, 1998, for a review), but systematic investigations of fetal perception did not get under way until the 1980s. How do you measure a fetal response to sounds? Usually, the investigators measure heart rate changes and sometimes body movements in response to differing types of sounds. These early studies provided evidence that by approximately 30 weeks' gestational age, a fetus hears and responds to simple sounds such as bursts of white noise. By 37–42 weeks, a fetus can discriminate between types of speech sounds (such as vowels, consonant-vowel syllables) (Lecanuet *et al*., 1987; Groome *et al*., 1999).

The finding that a fetus can both hear and discriminate between sounds before birth has led to investigations of what a fetus knows about specific sounds, namely, his or her own mother's voice. DeCasper and colleagues studied the listening preferences of newborn infants in a series of investigations in the 1980s. They found that newborns prefer their mother's voice to that of a female stranger (DeCasper and Fifer, 1980). These results led to a debate regarding the bases of speech perception: does a newborn's preference for his or her own mother's voice reflect a genetically pre-wired disposition for human language? Or does the newborn's preference reflect prenatal experience? A recent work by Kisilevsky and colleagues (Kisilevsky *et al*., 2003) advanced the results provided by DeCasper with more specific evidence that a late-term fetus recognizes the voice of his or her mother over the voice of a female stranger. They reported that the fetal heart rate *increases* when listening to the mother's voice and *decreases* when listening to a stranger's voice. While the findings of Kisilevsky and colleagues (Kisilevsky *et al*., 2003) do not resolve the nature versus nurture debate regarding the genetic or experience basis of a newborn's speech perceptual acuity, they provide intriguing evidence that a fetus can not only discern between familiar and unfamiliar voices, but suggests that before birth, there is a specific preference for the mother's voice.

There has recently been an increased focus on the effects of prenatal exposure to music. This focus is largely due to claims that prenatal exposure to music produces increases in intelligence or cognitive function as the baby develops. These claims are based on anecdotal information, however, with no rigorous scientific basis. Let's examine the evidence of what we do know about music perception at or near birth: there have been many infant studies investigating music perception abilities in the first months of life. Trehub and colleagues report that infants as young as 2 months old perceive rhythmic patterns in music. Further, Trehub reports that there are many parallels between early infant musical knowledge and adult patterns that appear to support some notion of an innate or at least a biological bias for music perception (see Trehub and Hannon, 2005, for a review).

Little is known about musical perception before birth. However, Kisilevsky and colleagues (Kisilevsky *et al*., 2004) have reported that late-term (33–37 weeks' gestational age) fetuses can discriminate between changes in tempo in musical sequences. Importantly, earlier term fetuses (28 weeks) did not show this effect, leading Kisilevsky to conclude that there are developmental changes *in utero* in music perception, with later term fetuses discriminating features in music that earlier term fetuses did not discriminate. Cumulatively, the research carried out by Kisilevsky and colleagues provides evidence that some higher order auditory perception for maternal voice and for music is not only occurring before birth, but is changing, maturing in its nature.

Does evidence that a fetus perceives human voice and music before birth rule out the idea of a genetic predisposition for language and music? Not really. The elucidation of the complex interactions between genetic expression and experience that underlie human speech and music perception are still being elucidated

in the field of developmental cognitive neuroscience. New techniques and experimental designs are being developed in order to address this very important question about human development.

3.0 THE DEVELOPING BRAIN: A LIFETIME OF CHANGE

3.1 The rise and fall of postnatal brain development

While the overall appearance of the newborn human brain is rather similar to that in adults, and most neurons have already reached their final locations, a number of substantive *additive* changes occur during postnatal development of the brain. Specifically, brain volume quadruples between birth and adulthood, an increase that comes from a number of sources, but generally not from additional neurons. The generation and migration of neurons takes place almost entirely within the period of prenatal development in the human. Although there may be some addition of neurons in the hippocampus and elsewhere, the vast majority are present by around the seventh month of gestation (Rakic, 1995).

Perhaps the most obvious change during postnatal neural development is the increase in size and complexity of the *dendritic trees* of most neurons. An example of the dramatic increase in dendritic tree extent during human postnatal development is shown in Figure 15.14. While the extent and reach of a cell's dendritic arbor may increase dramatically, it also often becomes more specific and specialized.

In addition to the more extensive processes involved in the inputs and outputs of cells, there is a steady increase in the density of synapses in most regions of the cerebral cortex in humans (Huttenlocher *et al*., 1982; Huttenlocher, 1990, 1994). The process of creating new synapses, *synaptogenesis*, begins approximately around the time of birth for all cortical areas studied to date, with the most increases, and the final peak density, occurring at different ages in different areas. For example, in the visual cortex there is rapid synaptogenesis at 3 to 4 months, and the maximum density of around 150 percent of that seen in adult humans is reached between 4 and 12 months. In contrast, while synaptogenesis starts at the same time in a region of the prefrontal cortex, density increases much more slowly and does not reach its peak until well after the first year.

Another additive process is *myelination*. Myelination refers to an increase in the fatty sheath that surrounds neuronal processes and fibers, that increases the efficiency of electrical transmission. Because myelination continues in cortical areas for many years after birth, there has been speculation about its role in behavioral development (Yakovlev and Lecours, 1967; Parmelee and Sigman, 1983; Volpe, 1987). Owing to the increased lipid content of the brain caused by myelination of fibers, structural MRI images can reveal a clear gray-white matter contrast and this allows quantitative volume measurements to be made during development (see Sampaio and Truwit, 2001). While some controversy remains about the interpretation of images from infants under 6 months, there is consensus that the appearance of brain structures is similar to that of adults by 2 years of age, and that all major fiber tracts can be observed by 3 years of age (Huttenlocher and Dabholkar, 1997; Bourgeois, 2001). Changes in the extent of white matter are of interest since they presumably reflect interregional communication in the developing brain. While increases in white matter extend through adolescence into adulthood, particularly in frontal brain regions (Huttenlocher *et al*., 1982), the most rapid changes occur during the first 2 years. Myelination appears to begin at birth in the pons and cerebellar peduncles and, by 3 months, has extended to the optic radiation and splenium of the corpus callosum. Around 8–12 months the white matter associated with the frontal, parietal, and occipital lobes becomes apparent.

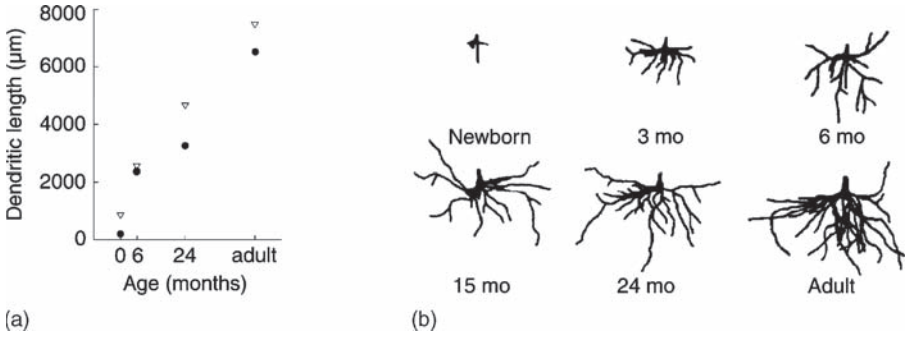


FIGURE 15.14 Dendritic arborization. A drawing of the cellular structure of the human visual cortex based on Golgi stain preparations from Conel (1939–1967). *Source*: Quartz, 1999, from Conel, 1953.

Surprisingly, human postnatal brain development also involves some significant *regressive events*. One quantitative neuroanatomical measure of a regressive event is the density of synapses, where there is a period of synaptic loss or *pruning* (Huttenlocher, 1990, 1994). Like the timing of bursts of synaptogenesis, and the subsequent peaks of density, the timing of the reduction in synaptic density appears to vary between cortical regions, at least in humans. For example, synaptic density in the visual cortex begins to returns to adult levels after about 2 years, while the same point is not reached until adolescence for regions of the prefrontal cortex. Huttenlocher (1990, 1994) suggests that this initial overproduction of synapses may have an important role in the apparent plasticity of the young brain.

Thus, the *rise and fall* developmental sequence is seen in a number of different measures of neuroanatomical and physiological development in the human cortex. However, we need to bear in mind that not all measures show this pattern (e.g. myelinization) and that measures of synaptic density are static snapshots of a dynamic process in which both additive and regressive processes are continually in progress.

While most of this section has focused on the cerebral neocortex, other brain structures, such as the hippocampus and cerebellum, also show some postnatal development. Indeed, the postnatal development of some subcortical structures (such as the hippocampus, cerebellum, and thalamus) poses something of a paradox; on the one hand there is much behavioral and neural evidence to indicate that these structures are functioning at birth, while on the other they all show some evidence of postnatal development and/or functional re-organization. One resolution of this puzzle is that as the cerebral cortex develops postnatally, its interactions with subcortical regions undergo certain changes. Thus, while some subcortical structures are capable of functioning relatively independently of the cortex early in life, the increasing development of the cortex requires some structural and functional adjustment.

3.2 Regional differences in brain development

As compared to other species, humans take a very long time to develop into independent creatures. Human postnatal cortical development, for example, is extended roughly four times as long as non-human primates. The 'down' side of this slow development is that there are many years during which a child is highly dependent on the care provided by family members. The 'up' side of this protracted developmental timetable is that the human brain has far more opportunity for experience, and interactions with others, to shape and mold its development.

As suggested above, the rise and fall pattern of additive and regressive events occurs at different time frames in regions and lobes in the human brain. These events are heavily experience driven and reflect synapse formation and dendritic arborization that are due to cognitive and sensory development, learning, and integrative processes that occur throughout infancy and childhood and continue through the teen years. A time course of brain development from conception to late teens is presented in Figure 15.15 (Casey *et al*., 2005). Prenatal changes are shown on the left side of the figure and largely reflect neurulation, cell proliferation, and migration processes. Postnatal changes reflect developmental processes such as synaptogenesis and dendritic arborization. Sensory areas for processing visual and auditory information, for example, develop earlier than frontal lobe regions such as the prefrontal cortex for processing executive functions (Casey *et al*., 2005).

How can we objectively measure brain development over the lifespan? One way in which to track developmental changes in the brain is to measure gray matter density across regions in the cortex. A large cross-sectional study of 176 subjects ranging in age from 7 to 87 years provided evidence for different patterns of gray matter density decrease across the lifespan (Toga *et al*., 2006). In the superior frontal sulcus, gray matter density decreases rapidly beginning in adolescence. However, in the superior temporal sulcus, gray matter density decreases more gradually through life (Figure 15.16).

While we are beginning to map out the developmental patterns for brain regions across the lifespan, a key issue that is being addressed is the notion of individual differences in how the brain matures and the correspondence to cognitive development. In other words, what is the relationship between brain and behavior? Do differing patterns of brain development reflect different levels of intellectual ability? These questions were addressed in a recent neuroimaging investigation of gray matter density in a large sample of more than 300 children and adolescents (Shaw *et al*., 2006). The sample was *a priori* divided into three groups based on their performance on an IQ battery of tests: 'Superior' with IQ ranging from 121 to 149; 'High' with IQ ranging from 109 to 120; and 'Average' with IQ ranging from 83 to 108. The results indicated that there are, indeed, differing patterns of brain change corresponding to overall level of intelligence (Figure 15.17). The notable finding was that high IQ was associated with thinner cortex, especially in frontal

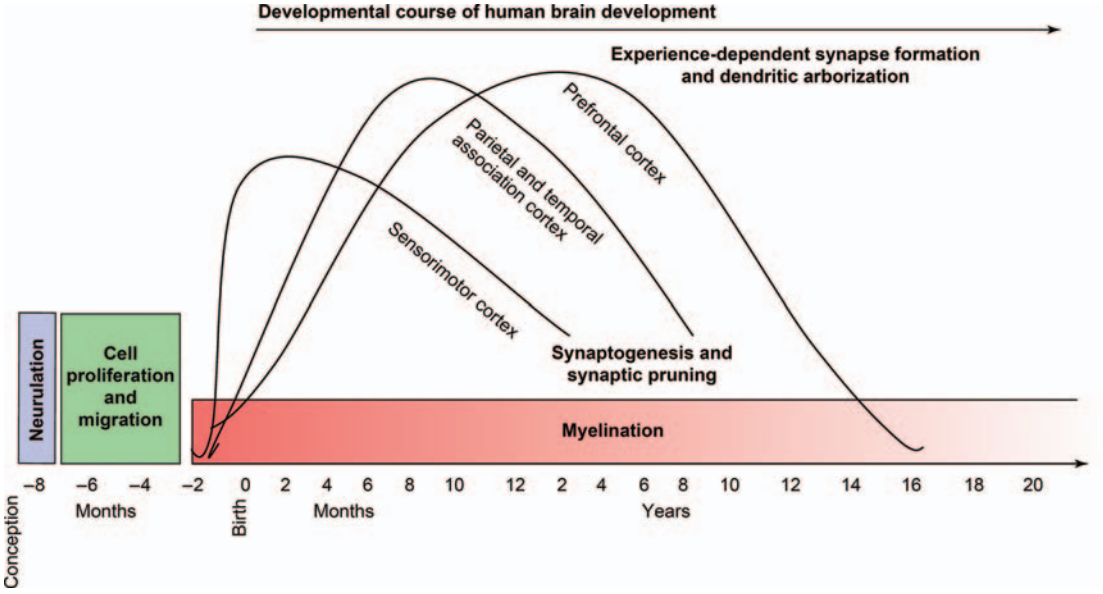


FIGURE 15.15 Developmental course of human brain development. The human brain undergoes dramatic changes in both its structural architecture and functional organization that reflect a dynamic interplay of simultaneously occurring progressive and regressive events. Although the total brain size is about 90 percent of adult size by age 6 years, the brain continues to undergo dynamic changes throughout adolescence and well into adulthood. Figure 15.15 illustrates some of these developmental changes, including proliferation and migration of cells mostly during fetal development, regional changes in synaptic density during postnatal development, and protracted development well into adulthood. Current non-invasive neuroimaging methods do not have the resolution to delineate which of these processes underlies observed developmental changes beyond gray and white matter subcomponents. (Adapted from Thompson and Nelson, 2001.) *Source*: Casey *et al.*, 2005.

and temporal lobe areas, in early childhood. By late childhood, the opposite pattern was found, with high IQ associated with thicker cortex.

The important finding of this study was that there was a differing pattern of cortical development in frontal lobe regions for children in the 'Superior' group as compared to either of the other groups. Specifically, there were differences in the dynamic rate of cortical thickening and thinning throughout early childhood and into adolescence and early adulthood. The authors concluded that differences in gray matter density in and of itself did not lead to children with superior intellectual abilities; rather they suggested that the dynamic properties of development of the cortex corresponded to level of intelligence, perhaps enabling the child to extract more information from his environment. Open issues raised by this study are dynamic changes in brain growth patterns due to genetic predispositions in the 'Superior' group? Or do they reflect differences in the environment? Or do they reflect a combination of both genetic influences and experience?

These findings from recent studies of brain development throughout the lifespan are helping us prepare new models for human cognitive growth and the correspondence to cognition. These studies are still very early work in an ongoing series of investigations of complex brain developmental processes. Although this investigation is still in its early stages, results to date provide evidence that the brain is changing in dynamic ways throughout early childhood and into adulthood.

4.0 DEVELOPING MIND AND BRAIN

We have seen that the brain undergoes significant developmental changes throughout childhood. An important question to address in the field of developmental cognitive neuroscience is how these brain changes reflect development of cognitive processes. New techniques are allowing us to begin to map brain development and the correspondence to cognition. The emergence of longitudinal multidisciplinary studies combining neuroimaging studies of cortical change and behavioral studies of performance on cognitive tasks will provide us with better ways to asses the relationship between brain development and cognition. In this section, we will discuss what we know at present about the relation between brain development and

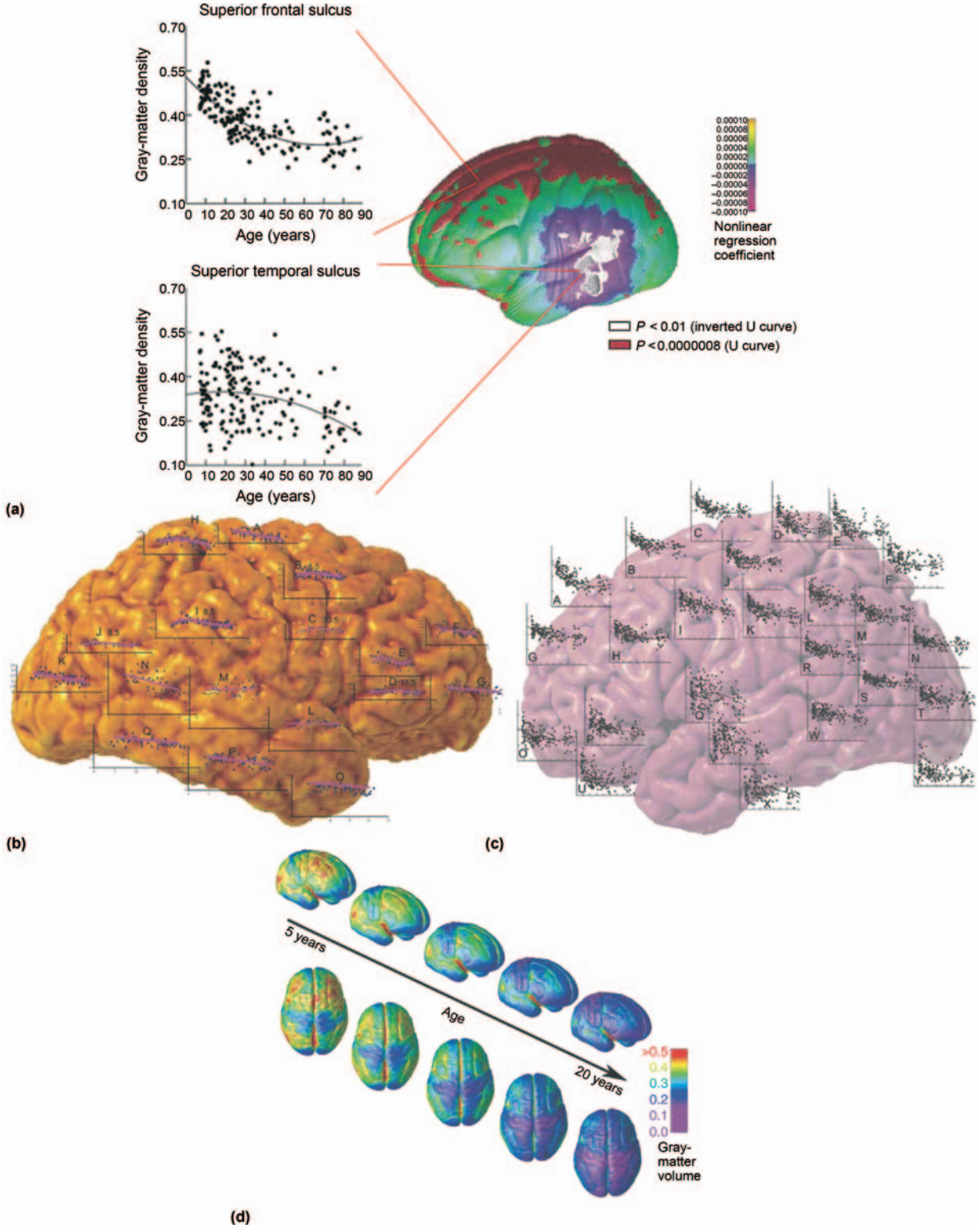


FIGURE 15.16 Mapping brain change over time. Brain changes in development can be identified by fitting time-dependent statistical models to data collected from subjects cross-sectionally (i.e. across a group of subjects at a particular time), longitudinally (i.e. following individual subjects as they aged), or both. Measurements such as cortical thickness are then plotted onto the cortex using a color code. (a, b) Trajectory of gray matter loss over the human lifespan, based on a cohort of 176 subjects aged 7 to 87 years (Sowell *et al.*, 2003). Plots superimposed on the brain in (b) show how gray matter density decreases for particular regions; (a) highlights example regions in which the gray matter density decreases rapidly during adolescence (the superior frontal sulcus) or follows a more steadily declining time course during the lifespan (the superior temporal sulcus) (c, d). *Source*: Toga *et al.*, 2006.

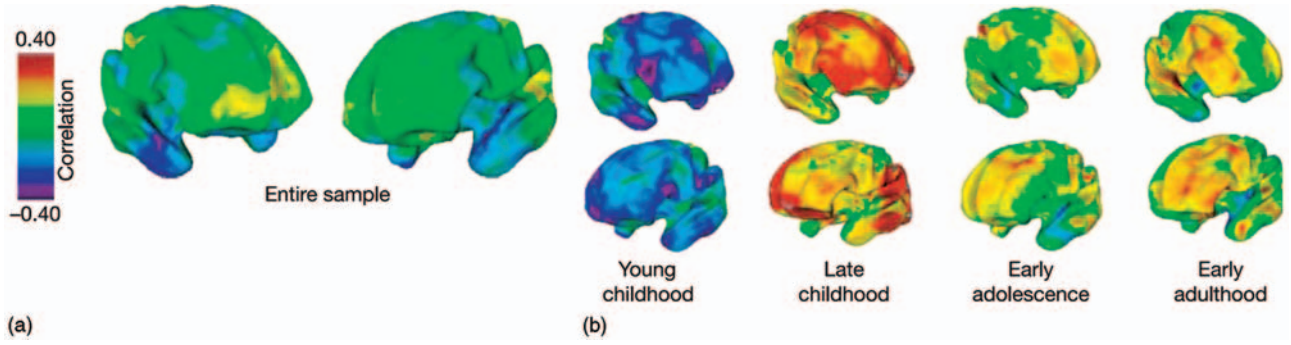


FIGURE 15.17 Correlations between IQ and cortical thickness. (a) Pearson's correlations for all 307 subjects were generally positive and modest ($p > 0.05$), with r between 0 and .10 (green/yellow), except in the anterior temporal cortex (which showed a negative correlation, with r between 0 and -1; blue/purple). (b) Correlations in different age groups showed that negative correlations were present in the youngest group, indicating that higher IQ was associated with a thinner cortex particularly in frontal and temporal regions. The relationship reverses in late childhood with most of the cerebral cortex correlating positively with IQ. *Source*: Shaw *et al.*, 2006.

FRONTIERS OF COGNITIVE NEUROSCIENCE

How babies learn

FIGURE 15.18 Jenny Saffran, PhD, Waisman Center, University of Wisconsin, Madison, WI, USA.

Speech is by far the most complex sound that humans decode. A central question for scientists who study human development is: How do infants learn to decode this complex signal?

You may have learned a new language in school during your adolescent or teen years. You were guided in this process by several factors that are not present for infants learning their first language: first, you were *aware* – conscious – that you were learning a new language; second, you could *relate* the new information to your existing knowledge of your first language (for example, you could learn that *agua* was the Spanish word for *water*); and third, you had a lot of *existing knowledge* about the structure of your language (for example, you know that individual sounds (phonemes) combine to form syllables and words).

Infants have none of this metalinguistic knowledge. They are simply highly motivated to interact with their family members and caregivers. So one wonders, how do infants learn to decode speech? How do they learn that the nearly continuous speech stream contains discrete words and phrases? In other words, how do infants extract word boundary information in speech?

Dr. Jenny Saffran at the University of Wisconsin, Madison, has some fascinating explanations for how infants accomplish this. Dr. Saffran theorizes that one important aspect of infant language learning is that infants unconsciously extract *statistical regularities* in the speech stream (Saffran *et al.*, 1996; Aslin *et al.*, 1998). Here is how she proposes it happens: within any given language, there are sound patterns that occur with some level of probability. Although all languages have many individual phonemes, sounds that are specific to that language, they form a finite set. And the way they are combined to form words—their phonology—is also constrained. Dr. Saffran theorizes that infants extract the *transitional probability* (TP) of sound patterns in speech (Figure 15.19). That is, the probability that a certain sound pattern will follow any given sound pattern, *conditioned on the probability* of the first sound pattern.

$$TP = P(Y|X) = \frac{\text{frequency (XY)}}{\text{frequency (X)}}$$

FIGURE 15.19 Schematic of an artificial grammar used by Saffran. *Source*: adapted from Saffran *et al.*, 1996, with permission.

For example, in English, the syllable 'ba' frequently is followed by the syllable 'by' to form the word 'baby' and this combination occurs with a much higher probability than the combination of 'ba' and 'sin' to form the word 'basin'. The TP of these combined syllables, then, is the probability of 'by' *given the probability* of 'ba', and the probability of 'sin' *given the probability* of 'ba'. And though the probability of the occurrence of 'ba' in the speech stream is the same, the TP differs sharply when combined with 'by' versus 'sin'.

According to Dr. Saffran, infants extract these probabilities and learn to form word boundaries using statistical learning mechanisms. Extracting the TPs in speech helps the infant to detect word boundaries and eventually to acquire language.

The work of Dr. Saffran and her colleagues has literally revolutionized the way developmental and language researchers think about infant learning processes. It has sparked a wave of new investigations, including new studies from the Infant Learning Laboratory directed by Dr. Saffran. Here are some 'threads' that are running through her current research in her Infant Learning Laboratory:

1. **Natural speech**: In her earlier work, Dr. Saffran used simplified stimulus sets and grammars to elucidate how infants develop speech perception. In her current set of studies, she is investigating infant learning processes using *natural language* stimuli. Results so far show that infants are as good or better at statistical learning in naturalistic speech (Pelucchi *et al.*, 2009).
2. **Real time learning**: The Saffran lab is looking at how infants learn in 'real time' by investigating the effects of statistical properties *as they are occurring*. Language comprehension in adults is facilitated by statistical information – knowing what is likely to come next. Dr. Saffran is currently testing the hypothesis that infants, too, make use of probabilistic information during language comprehension, as measured by eye-gaze tracking.
3. **Integrating across clinical populations**: The Saffran lab has been investigating how typically developing infants and children learn language. Now they are expanding their research to see if infants and children with language impairment or hearing loss learn language in a similar way (Evans *et al.*, 2009).

Although Dr. Saffran does not study the brain bases for these early-established infant learning mechanisms, her work raises intriguing questions: where are these mechanisms located in the infant brain? Do they represent domain general learning mechanisms that are invoked for language acquisition, but are also used in other cognitive development? Or are there multiple – and perhaps parallel – systems of learning that unite to form the scaffolding for knowledge and conceptual representation in infants and children? These questions remain open in the field of the cognitive neuroscience of child development so we shall have to wait to see what new studies tell us about brain mechanisms underlying infant learning!

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child developmental processes. While we highlight some recent studies, it is important to note that the field of developmental cognitive neuroscience is a very young one. The first fMRI studies of children were published in 1995 by Casey and colleagues (Casey *et al.*, 1995). Thus, while the findings we present here are informative, the answer to our questions regarding the neural bases of language acquisition, cognitive control processes, and social cognition are still being discovered in laboratories throughout the world.

We have discussed a functional framework for understanding the processes of cognition. Developmental cognitive neuroscientists are seeking to understand how these systems and processes that are observed in healthy adults (Figure 15.20) are developed and formed in infancy, childhood, and through adolescence. Once again, the question of the role of nature versus nurture is debated in the field. Is the human brain pre-wired for language? Face perception? Or are these processes based on experience throughout life? Since these topics are of

central interest in the study of human development, we will focus on three general areas of developmental cognitive neuroscience investigations that may shed light on these issues: the emergence of language; the development of cognitive control mechanisms; and the development of social cognition, with a specific focus on face perception. In the following section, we provide a brief summary of research to date on these topics in infants during the first year of life. Next, we present findings on these topics for older children and adolescents. Last, we review the effects of early (perinatal) brain damage on these systems.

4.1 The first year of life: an explosion of growth and development

The human brain increases fourfold in size from newborn to adult. Many of the dynamic changes that occur in development happen during the first year of life. During this 12-month span, an infant develops from a tiny creature with few voluntary movements to a busy toddler smiling, reaching for attractive objects, producing many speech sounds, crawling, and even walking as he or she explores the world.

4.1.1 Developing the linguistic brain: infant language capabilities

Remember the studies showing that babies can hear and discriminate their mother's voice before birth? Studies like these have provided compelling evidence that a newborn infant already has experience with human language. We have discussed the nature versus nurture debate regarding the genetic predisposition for language versus the role of experience. This debate has been influential in the field of developmental cognitive neuroscience, with many studies investigating just what an infant knows about language. Most studies of young infants (less than 12 months old) focus on the classes and categories of speech sounds: phonology. Studies with older infants and children also investigate semantic (meaning-based) and syntactic (grammar-based) knowledge.

Is language 'biologically special'? One way to begin to address this question is to see whether young babies are specifically sensitive to human speech. If there are specific neural correlates of speech processing observable very early in life, this may indicate language-related neural processing prior to significant experience.

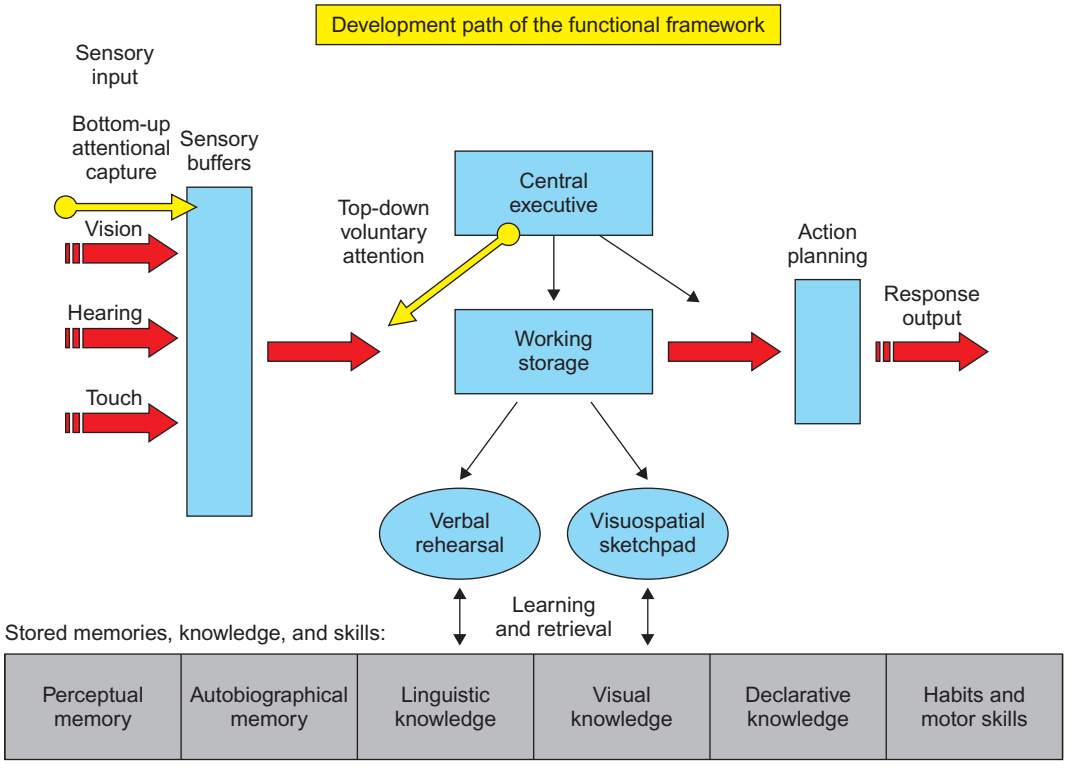

FIGURE 15.20 A functional framework for development, adapted from the general functional framework presented in Chapter 2.

One example of this approach concerns the ability to discriminate speech-relevant sounds such as *phonemes* (see Chapter 7). Each human language has a set of sounds that map onto individual phonemes, which typically are conscripted within slashes: /p/, for example, to reflect the sounds (phones) that map onto the phoneme /p/. Recall the 'lack of invariance' problem discussed in Chapter 7: the differing phonemes that are articulated before and after the articulation of /p/ affect its acoustic features. Thus, there is not a single invariant physical property that uniquely defines /p/. Rather, the representation of the phoneme /p/ must rely on some abstract (not just physical) features. This aspect of human speech has been exploited in speech perception studies where phonemes that differ in a single feature are prepared using speech synthesizing software to create a series of sounds that differ in graded steps between, for example, the phonemes /b/ and /p/, which differ only in their initial voicing (vocal chord vibration).

As English-speaking adults, if we were to listen to a graded phonetic transition from speech sounds 'ba' to 'pa', we would perceive the intermediates between /ba/ and /pa/ as being either one or the other. In other words, we show a *categorical boundary* between the two. Behavioral experiments have revealed that young babies also show enhanced (categorical) discrimination at phonetic boundaries used in speech such as /ba/ /pa/. That is, a graded phonetic transition from /ba/ to /pa/ is also perceived as a sudden categorical shift by infants. These observations initially caused excitement as evidence for a human speech perception–specific detection mechanism in humans. However, more recent research has shown that other species, such as chinchillas, show similar acoustical discrimination abilities. This indicates that this ability may merely reflect general characteristics of the mammalian auditory processing system and not an initial spoken language–specific mechanism (see Werker and Vouloumanos, 2001).

Intriguingly, and unlike adults, human infants can initially discriminate a very wide range of phonetic constructs, including those not found in their native language. For example, Japanese infants, but not Japanese adults, can discriminate between 'r' and 'l' sounds. However, this ability becomes restricted to the phonetic constructs found in their native language by around 10 months of age. These findings might reflect early speech perceptual processes that take into account the physical or acoustic features in all speech sounds in early infancy, developing later into mechanisms with less reliance on the physical aspects and more on the abstract representations of phonemes in their native language. In this way, the role of experience has a strong hand in shaping an infant's language knowledge.

If brain correlates of this process could be identified, it may be possible to study the mechanisms underlying this speech-specific selective decrease of sensitivity. Event-related potentials (ERPs) have been used to investigate this question. When components of ERP differ in both latency (following the event) and spatial resolution, we may be confident that different neural circuitry is being activated in the brain. Dehaene-Lambertz and Dehaene (1994) presented babies with trials in which a series of four identical syllables (the standard) was followed by a fifth that was either identical or phonetically different (deviant). They time-locked the ERP to the onset of the syllable and observed two peaks with different locations on the scalp. The first peak occurred around 220 ms after stimulus onset and did not habituate to repeated presentations (except after the first presentation) or dishabituate to the novel syllable. Thus, the brain generators of this peak, probably primary and secondary auditory areas in the temporal lobe, did not appear to be sensitive to the subtle acoustical differences that encoded phonetic information.

The second peak reached its maximum around 390 ms after stimulus onset and again did not habituate to repetitions of the same syllable, except after the first presentation. However, when the deviant syllable was introduced, the peak recovered to at least its original level. Thus, the neural generators of the second peak, also in the temporal lobe, but in a distinct and more posterior location, are sensitive to phonetic information. Further studies need to be carried out to ascertain whether the recovery of the second peak is due to the categorical perception of phonemes, or whether it would be elicited by any change in sound.

Further investigations by Dehaene-Lambertz and colleagues used two imaging methods with better spatial resolution to investigate early correlates of speech perception. For example, Dehaene-Lambertz *et al*. (2006) measured brain activation for forward and backward speech in 3-month-old infants. They found that forward and backward speech activated differing – although closely situated – brain areas in left temporal language areas (Figure 15.21). They also found that the forward speech activated right prefrontal cortex while the backward speech did not. Results provided evidence that as early as 3 months, infants show a left lateralization for speech that also activates frontal lobe regions.

The general conclusions from the above studies are reinforced by converging results from a new

methodology – near infrared spectroscopy (NIRS). In one experiment, Mehler and colleagues (Pena *et al*., 2003) played normal infant-directed speech or the same utterances played in reverse while they measured changes in the concentration of total hemoglobin within parts of the right and left hemisphere. They observed that left temporal areas showed significantly more activation when infants were exposed to normal speech than to backward speech or silence, leading them to conclude that neonates are born with a left hemisphere already biased for speech processing.

Language acquisition and speech perception have been some of the most active areas of developmental cognitive neuroscience. The use of converging methodologies, and frequent comparisons between typical and atypical trajectories of development, make it the domain most likely to see major breakthroughs over the next decade (see Gage *et al*., 2003a, b for a discussion of auditory mechanisms underlying speech development in children with autism disorder).

4.1.2 Developing the executive brain: what do babies know?

A critical aspect of an infant's cognitive growth during the first year of life is the ability to learn about his or her environment. New items will attract the attention of a young infant and he or she will gaze at these items for longer durations than for items that are accustomed to being seen. While it is important for an infant to gaze at a new item, it is also important for an infant to orient to other aspects of his or her environment. The trading effects of looking at new items and shifting attention to other elements in the world about them provides infants both with learning opportunities for understanding features in new items and a wide range of such experiences by changing the focus of their attention, both of which are critical to cognitive development.

The executive control for directing attention to new items, orienting, maintaining goals, and control over reaching movements are thought to require the most anterior portion of the brain, the prefrontal cortex (PFC) (see Chapter 12). As discussed earlier, the frontal cortex shows the most prolonged period of postnatal development of any region of the human brain, with neuroanatomical changes evident even into the teenage years (Huttenlocher, 1990; Giedd *et al*., 1999). For this reason, it has been the part of the brain most commonly associated with developments in cognitive abilities during childhood.

One of the most comprehensive attempts to relate a cognitive change to underlying brain developments has concerned the emergence of object permanence in infants. Object permanence is the ability to retain an object in mind after it has been hidden by another object or a cover (Figure 15.22). Specifically, Piaget observed that infants younger than around 7 months fail accurately to retrieve a hidden object after a short delay period if the object's location is changed from

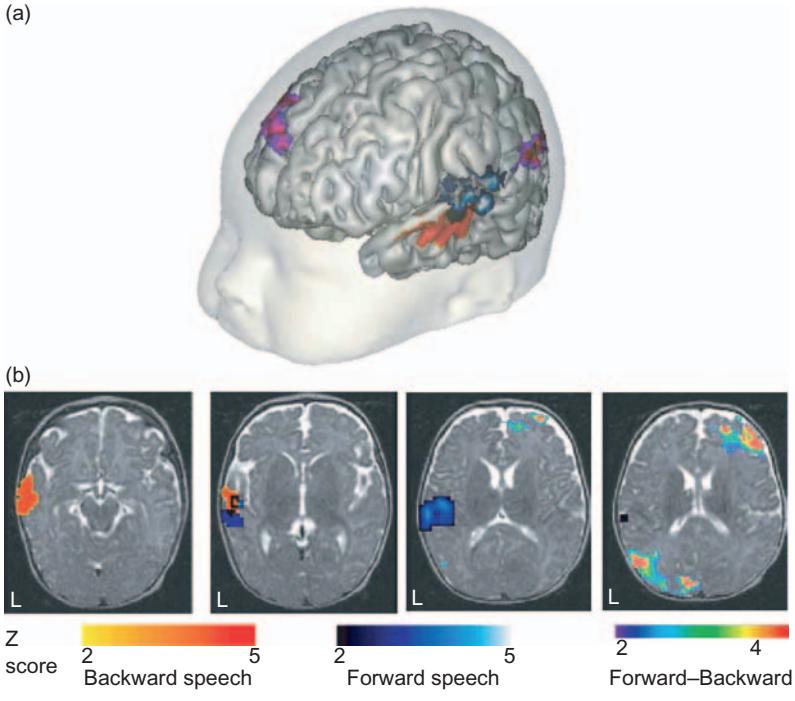

FIGURE 15.21 As early as 3 months, infants show a leftward laterality for human speech. Moving from left to right, the brain figures reflect (i) brain activation in the temporal lobe for backward speech (orange); (ii) brain response in a slightly higher brain slice, showing activation for both backward speech and forward speech (blue); (iii) brain response in a slightly higher brain splice showing activation for forward speech; (iv) the differing in brain activation for forward-backward speech shows activation in right prefrontal cortex. *Source*: Dehaene-Lambertz, *et al*., 2006.

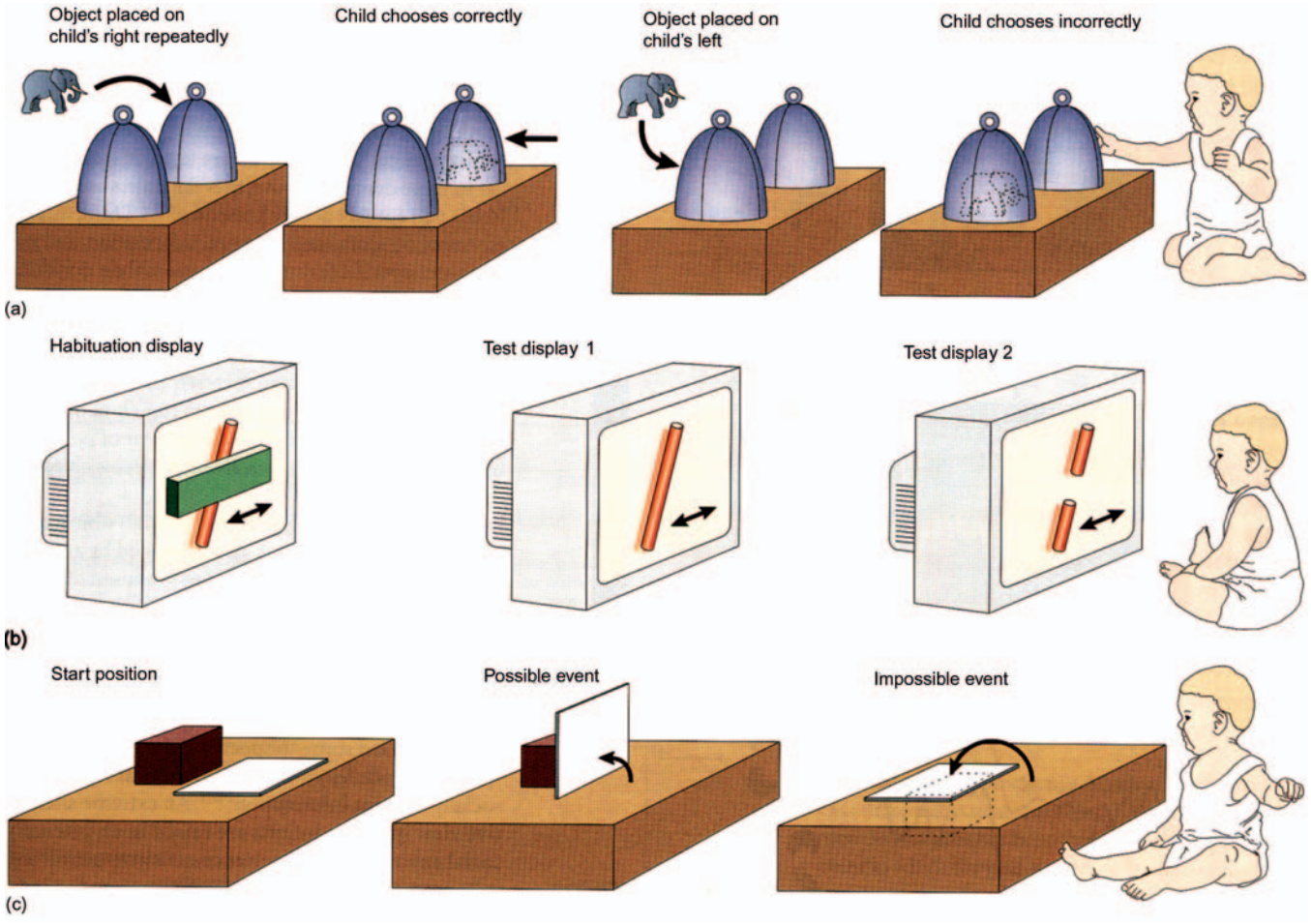

FIGURE 15.22 Behavioral testing in infants. (a) An object retrieval task that infants fail up to 9 months of age. In full view of the infant, the experimenter hides the object in one location and the infant reaches for it successfully. After a few such trials, the experimenter hides the object in a second place but the infant searches again at the original location (Piaget, 1954). (b) A visual habituation technique can be used to show that infants from as young as 4 months perceive the left-hand figure as a continuous rod moving behind an occluder. Infants dishabituated (found novel) the test display with two short rods, indicating that they perceptually 'filled in' the occluded area in the habituation display. Infants under 4 months are only partially successful in such tasks, depending on the complexity of the display. (c) The infant views two event sequences, one possible and one impossible, in which a flap is rotated toward a solid cube. In the 'possible' case the flap stops when it comes into contact with the object. In the impossible case the flap rotates through the object. Infants as young as 4 months appear surprised (look longer) when viewing the impossible event, showing that they appreciate that objects are solid and (usually) non-compressible. *Source*: Johnson, 2001.

one where it was previously and successfully retrieved. In particular, infants at this age make a particular perseverative error in which they persistently reach to the hiding location where the object was found on the immediately preceding trial. This characteristic pattern of error, called 'A not B', was cited by Piaget (1954) as evidence for the failure of infants to understand that objects retain their existence or permanence when moved from view. Beyond about 7 months infants begin to succeed in the task at successively longer delays of 1 to 5 seconds (Diamond, 1985, 2001).

Diamond and Goldman-Rakic (1989) found that infant monkeys also make errors in an adapted version of Piaget's object permanence task. Similar errors were also seen in adult monkeys with damage to dorsolateral prefrontal cortex (DL-PFC). Damage to other parts of cortex did not have the same effects, indicating a specific role for DL-PFC in this task.

Evidence linking this change in behavior to brain development also comes from EEG studies with human infants (Fox and Bell, 1990; Bell, 1992a, b; Bell and Fox, 1992). In these studies, increases in frontal EEG responses correlate with the ability to respond successfully over longer delays in delayed response tasks. Most recently, an optical imaging study with infants has revealed a correlation between behavioral

success at the AB task and blood oxygenation in prefrontal cortex (Baird *et al*., 2002).

Converging evidence for the importance of frontal cortex development comes from studies on children with an atypical neurochemical balance in the prefrontal cortex resulting from phenylketonuria (PKU) (Welsh *et al*., 1990; Diamond, 2001). Even when treated, this metabolic disorder can have the specific consequence of reducing the levels of a neurotransmitter, dopamine, in the dorsolateral prefrontal cortex. These reductions in dopamine levels in the dorsolateral prefrontal cortex result in these infants and children being impaired on tasks thought to involve prefrontal cortex such as the object permanence task, and having typical performance in tasks thought to be dependent on other regions of cortex, such as delayed non-matching to sample (Welsh *et al*., 1990; Diamond, 2001).

Thus, converging evidence from several sources supports the view that development of DL-PFC allows infants to succeed in the object permanence task. According to Diamond (1991), the critical features of the task carried out by DL-PFC is the ability to retain information over spatial delays and to inhibit prepotent (previously reinforced) responses. However, two recent lines of evidence suggest that the DL-PFC development hypothesis is not the whole story and that some modification or elaboration of the original account may be required. The first of these lines of evidence comes from another task thought to require DL-PFC: the oculomotor delayed response task (Figure 15.23). Gilmore and Johnson (1995) found that infants can succeed on this task at a much younger age than is indicated by the object retrieval tasks, even though it also requires the infant to maintain spatial information over a delay and needs to inhibit a prepotent response.

One explanation of the discrepancy between performance in Piaget's object permanence task and the results of Gilmore and Johnson (1995) is that tasks in which the response is an eye movement (looking) are easier since eye movement planning develops more rapidly than other forms of motor output such as reaching. This proposal is consistent with several studies showing that infants can perform successfully in analogous object permanence tasks as young as 4 or 5 months of age if looking rather than reaching performance is measured (Lecuyer *et al*., 1992).

In order to explain the difference between results obtained with eye movements as the measure and those with the manual reaching measures, it has been argued that infants do not yet have the necessary action planning skills to coordinate the sequence of motor

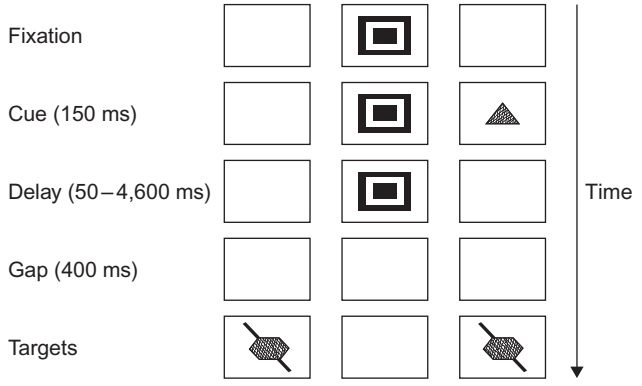

FIGURE 15.23 The oculomotor delayed response task as designed for use with infants. Infant subjects face three computer screens on which brightly colored moving stimuli appear. At the start of each trial a fixation stimulus appears on the central screen. Once the infant is looking at this stimulus, a cue is briefly flashed up on one of the two side screens. Following the briefly flashed cue, the central stimulus stays on for between 1 and 5 seconds, before presentation of two targets on the side screens. By measuring delayed looks to the cued location prior to the target onset, Gilmore and Johnson (1995) established that infants can retain information about the cued location for several seconds. *Source*: Gilmore and Johnson, 1995.

behaviors to retrieve a hidden object (Diamond, 1991; Baillargeon, 1993). To test this idea, Munakata *et al*. (1994) trained 7-month-old infants to retrieve objects placed at a distance from them by means of pulling on a towel or pressing a button. Infants retrieved objects when a transparent screen was interposed between them and the toy, but not if the screen was sufficiently opaque to make the object invisible. Since the same means-ends planning is required whether the screen is transparent or opaque, it was concluded that this cannot account for the discrepancy between the looking and the reaching tasks. Munakata *et al*. (1994) proposed an alternative 'graded' view of the discrepancy implemented as a neural network model. This model illustrates how weak internal representations of a stimulus can be sufficient to drive a simple output, such as an eye movement, but may be insufficient to initiate a more complex motor output, such as reaching.

An alternative approach to understanding the role of the prefrontal cortex in cognitive development has been advanced by several authors who have suggested that the region plays a critical role in the *acquisition* of new information and tasks. From this perspective, the challenge to the infant brain in, for example, learning to reach for an object, is equivalent in some respects to that of the adult brain when facing complex motor skills like learning to drive a car. Three predictions from this view are that (i) the cortical regions crucial for a particular task will change with

the stage of acquisition; (ii) the prefrontal cortex plays a role in organizing or allocating information to other regions of cortex; and (iii) that development involves the establishment of hierarchical control structures, with frontal cortex maintaining the currently highest level of control. Recent evidence showing PFC activation early in infancy has given further credence to this view. The limited number of fMRI and PET studies that have been done with infants have often surprisingly revealed functional activation in PFC, even when this would not be predicted from adult studies. For example, in an fMRI study of speech perception in 3-month-olds, Dehaene-Lambertz and colleagues (Dehaene-Lambertz *et al*., 2006) observed a right DL-PFC activation that discriminated (forward) speech in awake, but not sleeping, infants (Figure 15.21). Similar activation of DL-PFC was found in response to faces at the same age (Tzourio-Mazoyer *et al*., 2002). While this is evidence for activation of at least some of the PFC in the first few months, it remains possible that this activation is passive as it does not play any role in directing the behavior of the infant.

Developmental ERP studies have often recorded activity changes over frontal leads in infants and some experiments suggest that this activity has important consequences for behavioral output. These experiments involve examining patterns of activation that precede the onset of a saccade. In one example, Csibra and colleagues (Csibra *et al*., 1998, 2001) observed that pre-saccadic potentials that are usually recorded over more posterior scalp sites in adults are observed in frontal channels in 6-month-old infants. Since these potentials are time-locked to the onset of an action, it is reasonable to infer that they are the consequence of computations necessary for the planning or execution of the action.

Further evidence for the developmental importance of the PFC from early infancy comes from studies of the long-term and widespread effects of perinatal damage to PFC. Selective perinatal damage to the relevant regions activated in adults often has, at worst, mild effects on infants with subsequently nearly complete recovery of function. In contrast, perinatal damage to frontal and PFC regions often results in both immediate and long-term difficulties. This generalization from several domains suggests that PFC could play an important structuring or enabling role from very early in postnatal development.

The issue raised at the beginning of this section concerned how to reconcile evidence for continuing neuroanatomical development in the frontal cortex until the teenage years on the one hand, and evidence for some functioning in the region as early as the first few months of age on the other. One possible resolution to this issue is that representations that emerge within this region of cortex are initially weak and sufficient only to control some types of output, such as saccades, but not others, such as reaching (Munakata *et al*., 1994). Other plausible resolutions of this issue come from Diamond's (1991) proposal that different regions of frontal cortex are differentially delayed in their development, and Thatcher's (1992) suggestion that prefrontal regions may have a continuing role in the cyclical reorganization of the rest of cortex.

Whether these hypotheses work out or not, there is good reason why some degree of PFC functioning is vital from the first weeks of postnatal life, or even earlier (Fulford *et al*., 2003). The ability to form and retain goals, albeit for short periods, is essential for generating efforts to perform actions such as reaching for objects. Early and often initially unsuccessful attempts to perform motor actions provide the essential experience necessary for subsequent development.

4.1.3 Developing the social brain: faces and places

As described in Chapter 14, one of the major characteristics of the human brain is its social nature. A variety of cortical areas have been implicated in the 'social brain' including the superior temporal sulcus (STS), the fusiform 'face area' (FFA) and orbitofrontal cortex. One of the major debates in cognitive neuroscience concerns the origins of the 'social brain' in humans and theoretical arguments abound about the extent to which this is acquired through experience.

One aspect of social brain function in humans that has been the topic of many investigations is the perception and processing of faces. There is a long history of research on the development of face recognition in young infants extending back to the studies of Fantz more than 40 years ago (e.g. Fantz, 1964). Over the past decade, numerous papers have addressed the cortical bases of face processing in adults, including identifying areas that may be specifically dedicated to this purpose (see Chapter 6). Despite these bodies of data, surprisingly little remains known about the developmental cognitive neuroscience of face processing.

In a review of the available literature in the late 1980s, Johnson and Morton (1991) revealed two apparently contradictory bodies of evidence: while the prevailing view, and most of the evidence, supported the idea that infants gradually learn about the arrangement of features that compose a face over the first few months of life, the results from at least one study indicated that

BOX 15.1 Face preferences in newborns

Over the past decade more than a dozen papers have been published on the face-related looking preferences of newborn infants. Most of these papers concluded that newborns are biased to attend to stimuli that possess certain characteristics of faces, but two alternative views have been expressed.

The first of these views (the 'sensory hypothesis') is that all newborn visual preferences, including those for face-related stimuli, can be accounted for simply in terms of the relative visibility of the stimuli. The newborn visual system is restricted to the lower part of the range of spatial frequencies that is visible to adults. It has been proposed that newborns prefer to look at faces merely because the amplitude at different frequencies of these stimuli happens to best match the sensitivity of the newborn visual system. The sensory hypothesis has fallen out of favor because, even when amplitude is controlled, phase information (configuration) still influences the newborn preference toward faces. In addition, attempts to simulate newborn preferences with neural network models based on the sensory hypothesis are unlikely to account for other experiments involving realistic faces within the complex visual scenes to which newborns are exposed.

The second alternative view is that we have complex face processing abilities from birth. The findings used to support this claim include a preference for images of attractive faces, data indicating that newborns are sensitive to the presence of eyes in a face, and evidence that they prefer to look at faces that engage them in eye contact. In addition to the immaturity of the cortex at birth, all of these results could be accounted for by a low spatial frequency face configuration detector. For example, older infants prefer more attractive faces because these faces are closer to an average or prototypical face. Inspection of realistic face images through the appropriate spatial frequency filters for newborns reveals that a mechanism that is sensitive to the configuration of a face could be preferentially activated by (i) the most prototypical face configuration presented, (ii) the presence (or absence) of open eyes, and (iii) direct versus averted gaze (see Figure 15.23).

BOX 15.2 Why does the fusiform develop a face area?

A central debate in cognitive neuroscience concerns the origin and specificity of the fusiform face area (FFA) and other face-sensitive regions of cortex. One view is that the FFA is selectively activated by faces owing to genetically specified and domain-specific computational properties of that region. In contrast, others have proposed that the region is involved in processing visual stimuli in domains of perceptual expertise and most human adults become experts in face processing. From the developmental perspective taken in this chapter, an alternative 'middle way' account of FFA emerges. By this account, parts of the fusiform cortex become specialized for processing faces as a result of several constraining factors. First, the subcortical route described in this chapter ensures that newborns preferentially orient to faces and therefore foveate them, thus providing input to cortical visual pathways. Second, the cortical projection patterns of the subcortical route may enhance activation of specific areas, including the fusiform cortex, when faces are within the visual field of the young infant. Third, the parts of the fusiform cortex that become face sensitive receive foveal cortical visual input and are at the 'object-level' of visual stimulus processing in the ventral pathway. Thus, information from both face routes may converge in the FFA. These and other possible constraints, such as multimodal inputs and general biases in gene expression levels between the right and left cerebral cortex, combine to ensure that certain developing cortical circuits become specialized for face-related stimuli. By this developmental account it is inevitable, barring some disruption to the normal constraints, that parts of the fusiform cortex will specialize for faces. However, this inevitable outcome is achieved without genetically specified domain-specific patterns of connectivity with the FFA.

newborn infants, as young as 10 minutes old, will track a face-like pattern farther than various 'scrambled' face patterns (Goren *et al*., 1975). Evidence that newborns showed a preferential response to faces was used by some to bolster nativist views of infant cognition. In contrast, the evidence for the graded development of face processing abilities over several months tended to be cited by theorists who believed that such skills need to be learned, and result from experience of the world.

Although detailed issues remain, the finding that newborns preferentially respond to patterns that correspond to faces remains valid (see Johnson, 2005b, for review) (Figure 15.24). Recent evidence from a variety of sources indicates that there may be a subcortical route for face processing involving the superior colliculus, pulvinar, and amygdala (Johnson, 2005b). While this route is only evident in adults with functional imaging, or after acquired brain damage, it may be the main influence over the behavior of the newborn in which cortical routes for visual processing are relatively immature.

How may we investigate face perception in infants? Several laboratories have examined changes in

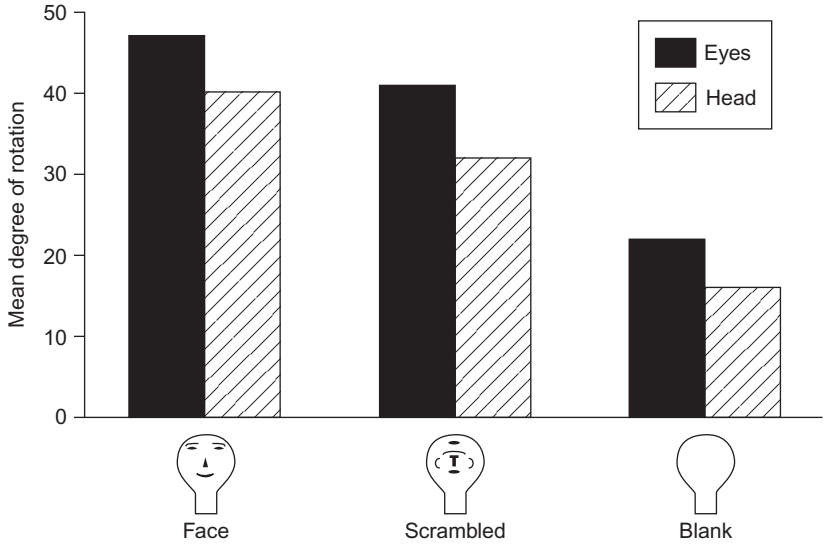

FIGURE 15.24 Face perception in newborns. Data showing the extent of newborns' head and eye turns in following a schematic face, a scrambled face, and a blank (unpatterned) stimulus. The infant tracked the face significantly farther than the other stimuli. *Source*: Johnson *et al.*, 1991.

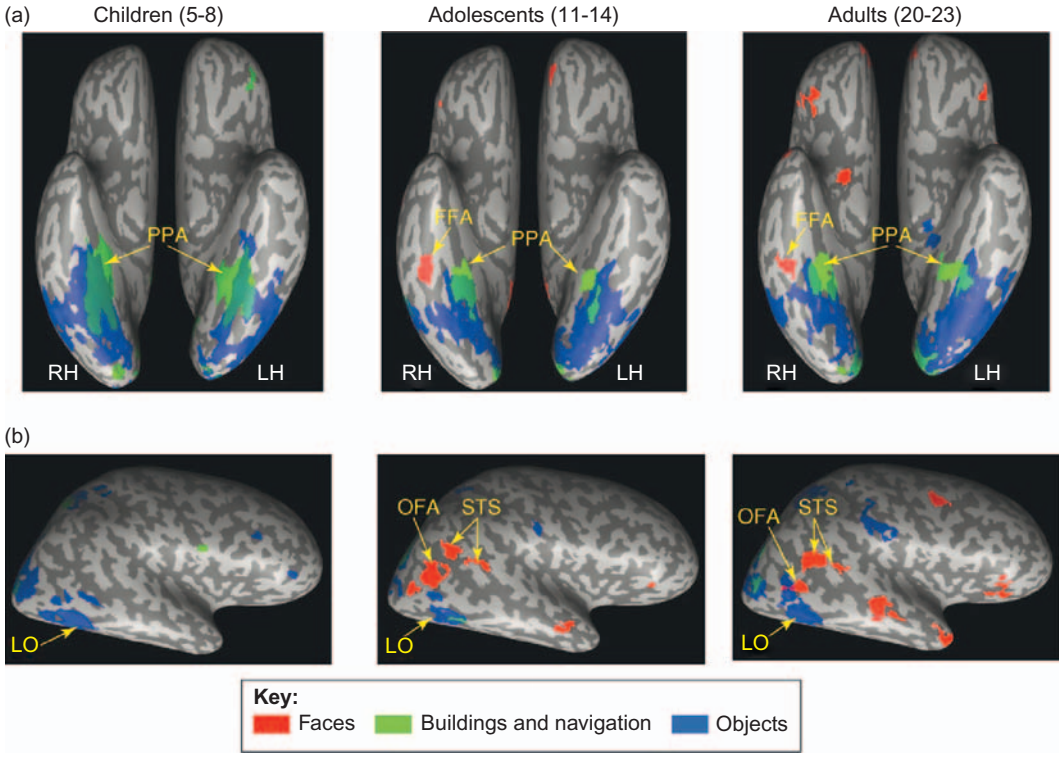

FIGURE 15.25 Brain activation for faces (shown in red), buildings (shown in green) and objects (shown in blue) for children 5–8 years (left panel), adolescents 11–14 years (center panel) and adults (right panel). Results showed that children 5–8 years did not sow the face selectivity of older adolescents and adults. *Source*: Kadosh and Johnson, 2007.

event-related potentials (ERPs) as adults view faces. In particular, interest has focused on an ERP component termed the 'N170' (because it is a negative-going deflection that occurs after around 170 ms) that has been strongly associated with face processing in a number of studies on adults. Specifically, the timing and size of this component vary according to whether or not faces are present in the visual field of the adult volunteer under study. An important aspect of the N170 in adults is that its response is highly selective.

For example, the N170 shows a different response to human upright faces than to very closely related stimuli such as inverted human faces and upright monkey faces. While the exact underlying neural generators of the N170 are currently still debated, the specificity of response of the N170 can be taken as an index of the degree of specialization of cortical processing for human upright faces. For this reason de Haan, Johnson, and colleagues (2002) undertook a series of studies on the development of the N170 over the first weeks and months of postnatal life.

The first issue addressed in these developmental ERP studies is when does the face-sensitive N170 emerge? In a series of experiments, a component was identified in the infant ERP that has many of the properties associated with the adult N170, but that is of a slightly longer latency (240–290 ms). In studying the response properties of this potential at 3, 6, and 12 months of age it was discovered that (1) the component is present from at least 3 months of age (although its development continues into middle childhood), and (2) the component becomes more specifically tuned to human upright faces with increasing age. To expand on the second point, it was found that while 12-month-old infants and adults showed different ERP responses to upright and inverted faces, 3- and 6-month-old infants do not. Thus, the study of this face-sensitive ERP component is consistent with the idea of increased specialization of cortical processing with age, a result also consistent with recent functional neuroimaging studies.

In a study by Sherf and colleagues (Sherf *et al*., m 2007), played movie clips of faces, objects, and buildings to children (5–8 years), adolescents (11–14 years) and adults. They found that the children did not show face specific brain activation (Figure 15.25). This finding provides evidence that although face processing may have an initial bias in neural processing, experience plays a key role in the development of face-selective cortex (Kadosh & Johnson, 2007).

Converging evidence about the increasing specialization of face processing during development comes from a behavioral study that set out to test the intriguing idea that, as processing 'narrows' to human faces, infants will lose their ability to discriminate non-human faces. Pascalis and colleagues (Pascalis *et al*., 2002) demonstrated that while 6-month-old infants could discriminate between individual monkey faces as well as human faces, 9-month-old infants and adults could only discriminate the human faces. These results are particularly compelling since they demonstrate a predicted competence in young infants that is not evident in adults.

Moving beyond the relatively simple perception of faces, a more complex attribute of the adult social brain is processing information about the eyes of other humans. There are two important aspects of processing information about the eyes. The first of these is being able to detect the direction of another's gaze in order to direct your own attention to the same object or spatial location. Perception of averted gaze can elicit an automatic shift of attention in the same direction in adults, allowing the establishment of 'joint attention'. Joint attention to objects is thought to be crucial for a number of aspects of cognitive and social development, including word learning. The second critical aspect of gaze perception is the detection of direct gaze, enabling mutual gaze with the viewer. Mutual gaze (eye contact) provides the main mode of establishing a communicative context between humans and is believed to be important for normal social development. It is commonly agreed that eye gaze perception is important for mother-infant interaction and that it provides a vital foundation for social development.

In a series of experiments with 4-month-old infants using a simple eye gaze cueing paradigm, Farroni and colleagues (Farroni *et al*., 2000) have established that it is only following a period of mutual gaze with an upright face that cueing effects are observed. In other words, mutual gaze with an upright face may engage mechanisms of attention such that the viewing infant is more likely to be cued by subsequent motion. In summary, the critical features for eye gaze cueing in young infants are (1) lateral motion of elements and (2) a brief preceding period of eye contact with an upright face.

Following the surprising observation that a period of direct gaze is required before cueing can be effective in infants, the earliest developmental roots of eye contact detection have been investigated. It is already known that human newborns have a bias to orient toward face-like stimuli (see earlier), prefer faces with eyes opened, and tend to imitate certain facial gestures. Preferential attention to faces with direct gaze would provide the most compelling evidence to date that human newborns are born prepared to detect socially relevant information. For this reason we investigated eye gaze detection in humans from birth. Farroni and colleagues tested healthy human newborn infants by presenting them with a pair of stimuli, one a face with eye gaze directed straight at the newborns and the other with averted gaze. Results showed that the fixation times were significantly longer for the face with the direct gaze. Further, the number of orientations was higher with the straight gaze than with the averted gaze.

In a second experiment, converging evidence for the differential processing of direct gaze in infants was obtained by recording event-related potentials (ERPs) from the scalp as infants viewed faces. Farroni and colleagues studied 4-month-old babies with the same stimuli as those used in the previous experiment with newborns and found a difference between the two gaze directions at the time and scalp location at the previously identified face-sensitive component of the infant ERP discussed earlier. The conclusion from these studies is that direct eye contact enhances the perceptual processing of faces even in infants as young as 4 months.

Beyond face processing and eye gaze detection, there are many more complex aspects of the social brain, such as the coherent perception of human action and the appropriate attribution of intentions and goals to conspecifics. Investigating the cognitive neuroscience of these abilities in infants and children will be a challenge for the next decade. One way in which these issues have been addressed is through studying genetic developmental disorders in which aspects of social cognition are either apparently selectively impaired (autism) or, selectively intact amid otherwise impaired cognition (Williams syndrome).

The first year of life brings dynamic changes in both behavior and the brain. While we provided separate discussions of the emergence of language, executive functions, and social cognition in this busy first year of life, these three domains of human cognition have complex interactions throughout development. An infant's interest in faces, for example, will help him or her to understand speech. The ability to focus on new objects aids the infant in developing knowledge about the world around him or her. While we do not fully understand the explosive growth of brain processes and their relation to behavior in infants, studies such as the ones we presented here are helping to map the complex correspondence between mind and brain.

4.2 Childhood and adolescence: dynamic and staged growth

While the first year of life represents an unparalleled stage in dynamic human development, many aspects of brain and cognitive growth take years to mature. As we mentioned earlier, the field of developmental cognitive neuroscience is a young one. In this section, we will present results from some studies investigating the development of brain areas subserving language, executive functions, and social cognition in children and adolescents and its relation to behavior. While these studies are informative, it is important to bear in mind that relating complex brain activation to performance on cognitive tasks is a highly complex process. For example, it may well be the case that the brain activity that we observe in adults – once a cognitive process has been developed – may tap differing brain regions while it is being acquired. Thus, simply comparing regions of interest in neuroimaging experiments across groups of children versus adults may not provide us with the level of sensitivity that we require in order to formulate inferences about brain and behavior. Similarly, differing cognitive strategies or coping mechanisms in childhood versus adulthood may also impact the network of brain areas tapped in certain task paradigms.

With those caveats in mind, let's review the evidence regarding the development of neural systems for language, executive control, and social cognition.

4.2.1 The linguistic brain: language acquisition

Language is not a unitary system: in order to express our ideas verbally, we need to progress through stages of formulating the concepts, mapping them onto words in our mental lexicon, accessing our mental grammar to form sentences, and mapping this information onto sound-based representations of the articulation of the ideas we want to express. Thus, the language system has multiple stages of computation across many categories or aspects of language. It makes intuitive sense that, early in life, infants develop their knowledge about language based largely on the sounds of language that they hear in their environment. Thus, it is not surprising that studies with young infants (less than 12 months) typically focus on the phonology of human language. With older infants, children, and adolescents, studies typically test other aspects of language such as lexical-semantic (meaning based) and syntactic (grammar based) knowledge.

Do all aspects of language develop in similar ways, with similar brain developmental processes underlying them? This is a question that has been addressed by developmental cognitive neuroscientists investigating the neural substrates of human language. Here is a brief summary of what we have learned so far.

We have previously discussed the use of event-related potentials (ERPs) for measuring the time course of human brain response for stimulus events. Several ERP components have been used to investigate language emergence in infants and young children and we describe them here:

- The mismatch negativity (MMN) component: this component shows a negativity at 100–250 ms

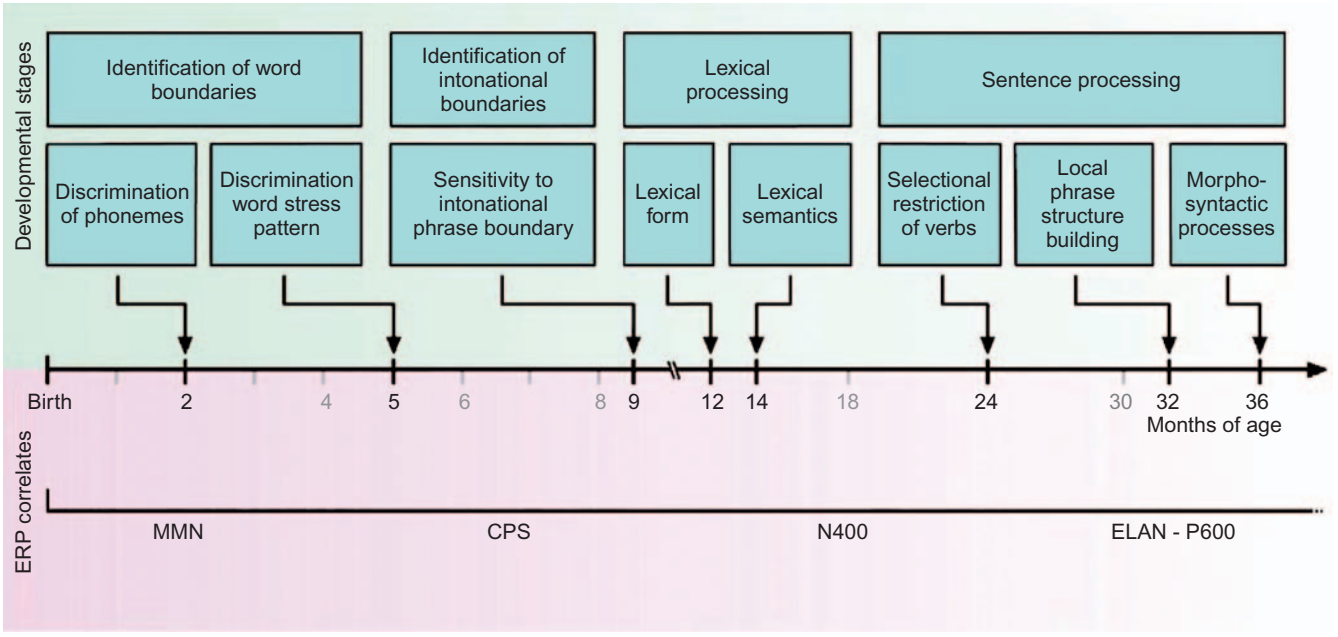

FIGURE 15.26 A schematic overview of the developmental stages of auditory language perception and the ERP correlates that provide the possibility to investigate phonological, semantic and syntactic processes. The developmental stages can be viewed as interrelated steps during which novel information is extracted and processed on the basis of previously acquired knowledge. Once the basic phonological processes are established, phonemic knowledge is used to identify and represent the first lexical forms and create a larger lexical semantic knowledge base, which is then used to process meaning in sentential context. The depicted time course of the different developmental stage is an approximation and is based on the ERP studies available in the literature. This also holds for the relation between the developmental age and the ERP components reported in the different studies discussed in the text. *Source*: Friederici, 2005.

which reflects the ability for the brain to discriminate between acoustic/phonetic features in sounds

- The N400, a negativity at ~400 ms which has source generators in centro-parietal regions. The N400 is thought to reflect lexical-semantic processes in word and sentence comprehension
- A left anterior negativity (E/LAN) which occurs ~150–350 ms and reflects online syntactic processes
- The P600, a positive deflection at ~600 ms with a centro-parietal distribution of sources. The P600 reflects processes engaged in syntactic revision and reanalyses.

Friederici (2005) describes the time course of language development in infants and children in a recent review of the child language literature (Figure 15.26). According to this review, phonological and intonational processes develop relatively early (birth to 9 months) while lexical, semantic, and syntactic processes develop somewhat later (1–3 years) as infants and young children acquire information at word and sentence levels.

During the first 2 years of life, there is an explosion of language knowledge and abilities as the infant begins to babble, produce simple sounds ('mama'), words ('dog'), and two- to three- word utterances ('want juice'). By age 2, a child can typically produce many words. But what does a 2-year-old understand about the meaning of words? Are they simply mimicking words/sounds they have heard? Or do they have knowledge beyond simple repetition of sound? Researchers have devised clever experimental procedures to investigate the semantic knowledge of infants and young children. One method is to present a picture of an object that the child is familiar with, for example, a duck, following by the word 'duck' (congruous condition) or a word that does not match the picture ('cat', incongruous condition). These careful testing procedures have enabled language researchers to test very young children in order to elucidate their level of semantic knowledge. Results of one such study are presented in Figure 15.27, providing evidence that infants as young as 14 months have semantic contextual knowledge, reflected in N400 responses for congruous and incongruous events (Friederici, 2005).

What do 2-years-olds know about the grammatical rules of their language? Sentence level processing was investigated in a sample of 2-years-olds and adults by contrasting sentences that were grammatically well formed ('The lion roars') to sentences that

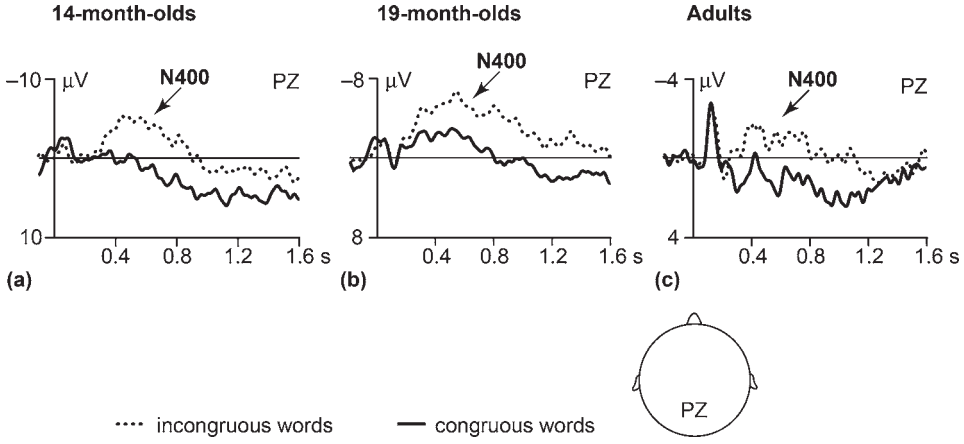

FIGURE 15.27 Semantic processing to congruous and incongruous words. The brain response of (a) 14 months old, (b) 19 months old, and (c) adults in a picture priming paradigm. A picture was presented for 4 s on a screen and 900 ms after the picture onset an indefinite article was acoustically presented, followed 1 s later by a word that was either congruous with the picture (e.g. a picture of a duck followed by the word 'duck') or not (a picture of a duck followed by the word 'cat'). The solid line represents the ERP to the congruous word condition and the broken line to the incongruous word condition. ERPs shown for one selected electrode (Z) – a negativity starting around 400 ms (N400) is observable in all age groups. ((a) Adapted with permission from Friedrich and Friederici, 2005. (b,c) adapted from Friedrich and Friederici, 2005). *Source*: Friederici, 2005.

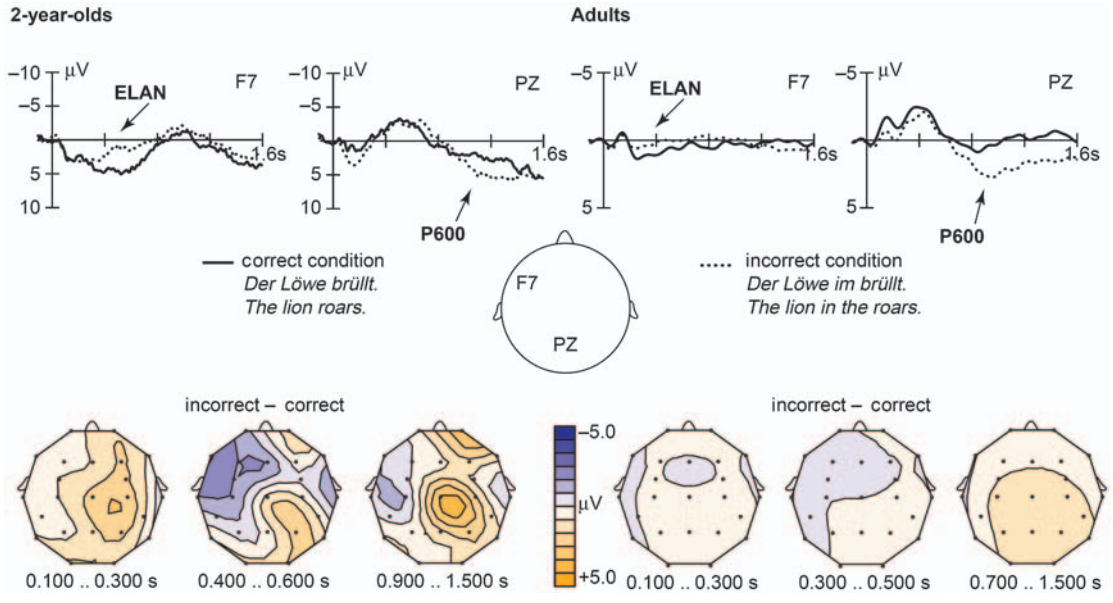

FIGURE 15.28 Syntactic processes in 2-year-olds. (a) Brain responses of 2-year-old children and adults to phrase structure violations in simple active sentences. ERPs are shown for the critical last word in the syntactically correct condition (solid line) and the syntactically incorrect condition (broken line), from the word onset for two selected electrodes (F7, PZ). An early left anterior negativity (ELAN) and a late positivity (P600), both known to be elicited in adults in response to phrase structure errors, were also observed for 2-year-old children. (b) Topographic maps showing the difference in brain activation when the correct condition is subtracted from the incorrect condition, indicating the topographical distribution of the effects in 2-year-olds (left) and adults (right). (Adapted from Oberecker *et al.*, 2005). *Source*: Friederici, 2005.

were not grammatical ('The lion in the roars'). The 2-years-olds were able to discriminate between well-formed and ill-formed sentences, as indexed by the E/LAN and P600 components (Figure 15.28).

How do these ERP studies inform us about brain processes for language acquisition in childhood? While these types of studies are in their early stages, these investigations reflect developments in ERP

recording techniques and experimental designs that are effective at providing sensitive measures of early language knowledge. While more work is needed to understand fully the complexities of human language acquisition, these studies provide important new data about language knowledge in very young children.

Cortical brain areas develop throughout childhood and adolescence, as mentioned in earlier sections of this chapter. How do brain regions for speech perception and production develop and mature in childhood? Classical brain areas for language include a frontal lobe region (functionally identified as Broca's area) and a temporal lobe region (functionally known as Wernicke's area) that subserve speech production and perceptual processes. Throughout childhood, these regions become connected through the experiences of producing and perceiving auditory language. A study by Paus and colleagues (Paus *et al.*, 1999) used fMRI to investigate the development of connections between Broca's area and Wernicke's area using white matter density measures in a large sample (N = 111) of children in the age range 4–11 years. Their results show age-related changes in the internal capsule (Figure 15.29, left panel) and the left arcuate fasciculus, the fiber tract thought to connect Broca's and Wernicke's areas in the left hemisphere (Figure 15.29, right panel).

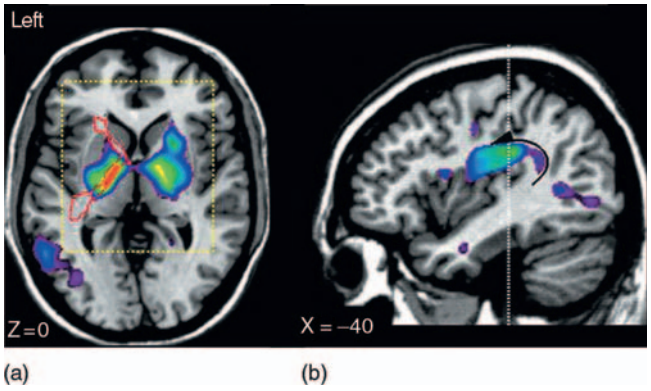

FIGURE 15.29 Age related changes in white matter in two regions in the brain. An increase in white matter density was shown for the internal capsule (left panel) and the arcuate fascinulus in the left hemisphere (right panel) in a sample of 111 children age 4–17 years. (Reprinted with permission from Paus *et al.*, 1999.) *Source*: Paus *et al.*, 2005.

Recall that measures of cortical thickness have been used to investigate patterns of development in cortex. Are there specific changes in anatomical brain regions that support language function? Toga and colleagues (Toga *et al.*, 2005) investigated this using a longitudinal approach in a sample of 45 typically developing children studied between the ages of 5 and 11 years. Cortical thickening increases of ~0.10–0.15 mm/year were found in brain regions corresponding to Broca's and Wernicke's areas (Figure 15.30).

Does this evidence for cortical thickening in brain regions subserving language reflect the ongoing and dynamic changes in child language? It is likely the case, but more studies relating these anatomical changes to language ability must occur before we fully understand the mind-brain correspondence in the development of language.

In this section, we have highlighted evidence that very young children have sophisticated knowledge about semantic and syntactic information in spoken language. We have also shown that language regions in the brain continue to develop throughout childhood and into adolescence. However, there are many questions

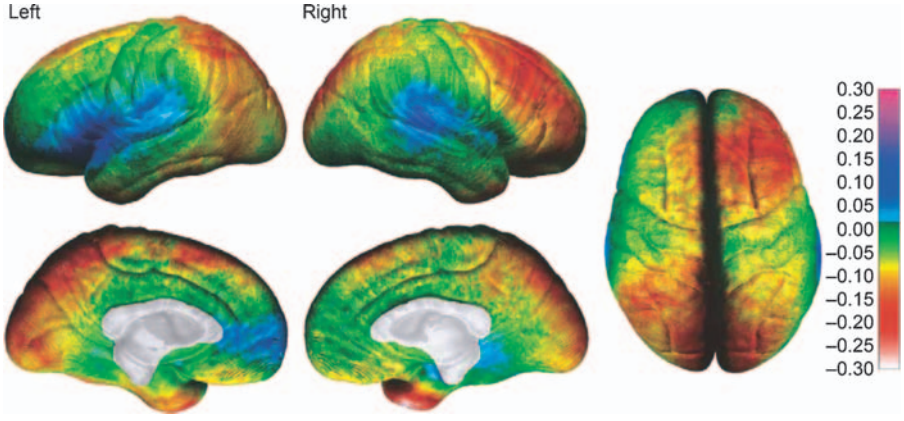

FIGURE 15.30 Annualized rate of change in cortical thickness. The average rate of change in cortical thickness is shown in millimeters according to the color bar on the right (maximum gray matter loss is shown in shades of red and maximum gray matter gain is shown in shades of blue). Forty-five children were studied twice (two-year scan interval) between 5 and 11 years of age. *Source*: Toga *et al.*, 2005, from Sowell *et al.*, 2004, with permission.

that remain unanswered regarding language acquisition. A central issue that remains unresolved is the trading relationship between nature (genetic predisposition for language) and nurture (the role of experience). Other aspects of language acquisition that are currently under investigation are the development of language systems in children who are bi lingual or multi lingual.

4.2.2 The executive brain: taking cognitive control

Even young infants must learn what information in their world is important and what is unimportant or irrelevant. These learning mechanisms fall under the general category of 'cognitive control' and have been the focus of much study in infant and child development. Recall that, in infants, the A not B task has been used to investigate the ability to ignore or inhibit irrelevant information and to inhibit prepotent response (Piaget, 1937, 1954; Diamond, 1985). These capabilities become more and more important throughout childhood as a child's environment becomes increasingly complex. Consider a 6-year-old child in a first grade classroom: this child must be able to attend to the teacher or to a task at hand despite the many distractions that surround him, such as children talking, books dropping, chairs scraping. The trading of attentional resources toward relevant aspects of the environment and away from less important aspects is a vital element in development.

In adults, the DL-PFC is implicated as an important cortical region in tasks that tap cognitive control functions. We know from histological and neuroanatomical studies of developing children that the PFC has a prolonged developmental path, not reaching mature, adult-like stages until mid- to late adolescence. Behavioral studies of cognitive control function in children and adolescents have provided evidence for a similar time course in the development of cognitive control abilities. An open question in the field of developmental cognitive neuroscience is there correspondence between these late-to-mature brain regions and the late developing cognitive control abilities?

Studies of the neural substrates of cognitive control have only recently been undertaken with children. Casey and colleagues (see Casey *et al.*, 2005, for a review) have conducted seminal studies of cognitive control using a combination of fMRI and behavioral methods in order to investigate the neural patterns of brain activation measured while children perform tasks likely to engage PFC regions. In one experiment, they used event-related fMRI while children and adults were engaged in a 'go-no go' task (Durston *et al.*, 2002). In this task, participants had to suppress their response when presented with a particular visual item within an ongoing sequence of stimulus presentations (e.g. one Pokemon character within a sequence of other Pokemon characters). The difficulty of the task was increased by increasing the number of 'go' items that preceded the 'no go' character. Successful response inhibition was associated with stronger activation of prefrontal regions for children than for adults. Also, while in adults the activation of some prefrontal

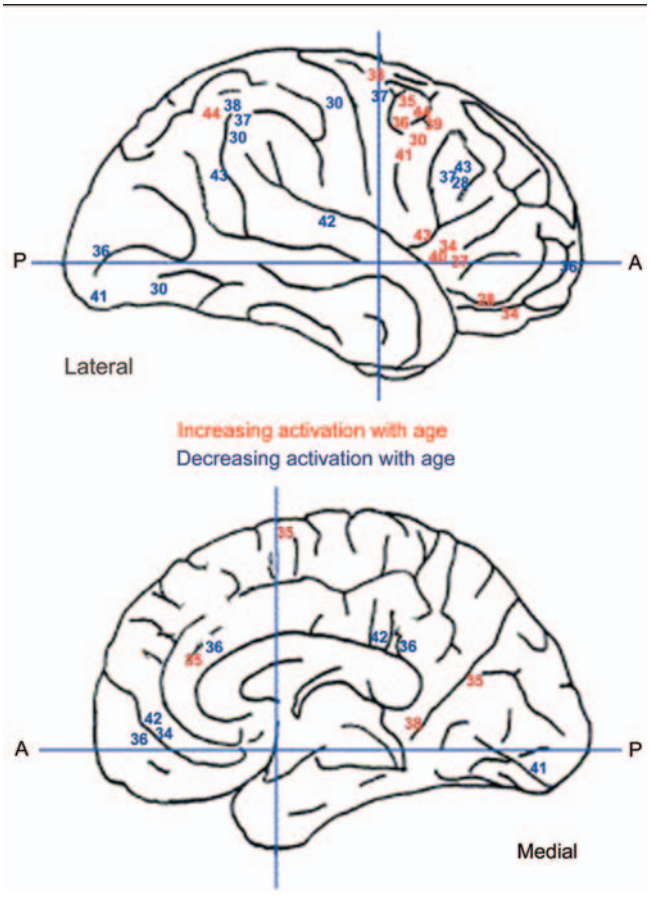

FIGURE 15.31 The development of human cortical function, as measured by contemporary imaging methods, reflects fine-tuning of a diffuse network of neuroanatomical regions. Collectively, developmental neuroimaging studies of cognitive control processes suggest a general pattern of increased recruitment of slow maturing prefrontal cortex (references depicted here in red), especially dorsolateral prefrontal cortex and ventral prefrontal cortex, and decreased recruitment of lower level sensory regions (references in blue), including extrastriate and fusiform cortex and also posterior parietal areas. Importantly, specific activations vary with task demands, so working memory and Stroop tasks recruit different regions from response inhibition tasks. This pattern of activity, which has been observed across a variety of paradigms, suggests that higher cognitive abilities supported by association cortex become more focal or fine-tuned with development, whereas other regions not specifically correlated with that specific cognitive ability become attenuated. A = anterior; P = posterior. *Source*: Casey *et al.*, 2005.

regions increased with increasing numbers of preceding 'go' trials (consistent with increasing need for inhibition), in children the circuit appeared to be maximally active for all trial types. Along with the poorer behavioral performance of children in this and other inhibitory tasks, these findings suggest that the functional development of some PFC regions is important for the mature ability to inhibit prepotent tendencies.

A general finding of Casey and colleagues has been that younger children exhibit broader, more diffuse brain activation for cognitive control tasks as compared to adults. During development, these brain areas mature and the brain activity that correlates to task performance abilities (such as reaction time and accuracy) become more focal and fine-tuned. In Figure 15.31, we present a figure from a recent article by Casey and colleagues (Casey *et al*., 2005) reviewing the literature of developmental cognitive control investigations. The general notion of brain activation becoming more focal and defined as a function of a child's age is shown with references to those studies showing increased activation with age and those showing decreased activation with age.

Another approach to elucidate the role of frontal circuits in tasks that tap cognitive control functions was provided in a recent fMRI study of children aged 8–12 years (Konrad *et al*., 2005). Konrad and colleagues utilized a well-accepted model for adult attentional processes (Posner and Petersen, 1990) and combined it with a task that has been well described in how it engages attentional processes, the Attention Network Task (ANT) (Fan *et al*., 2002) (Figure 15.32).

The attention model proposed by Posner and colleagues describes differing (separable but highly overlapping) neural networks for:

1 alerting to new and relevant information
2 orienting and reorienting to relevant information or stimuli

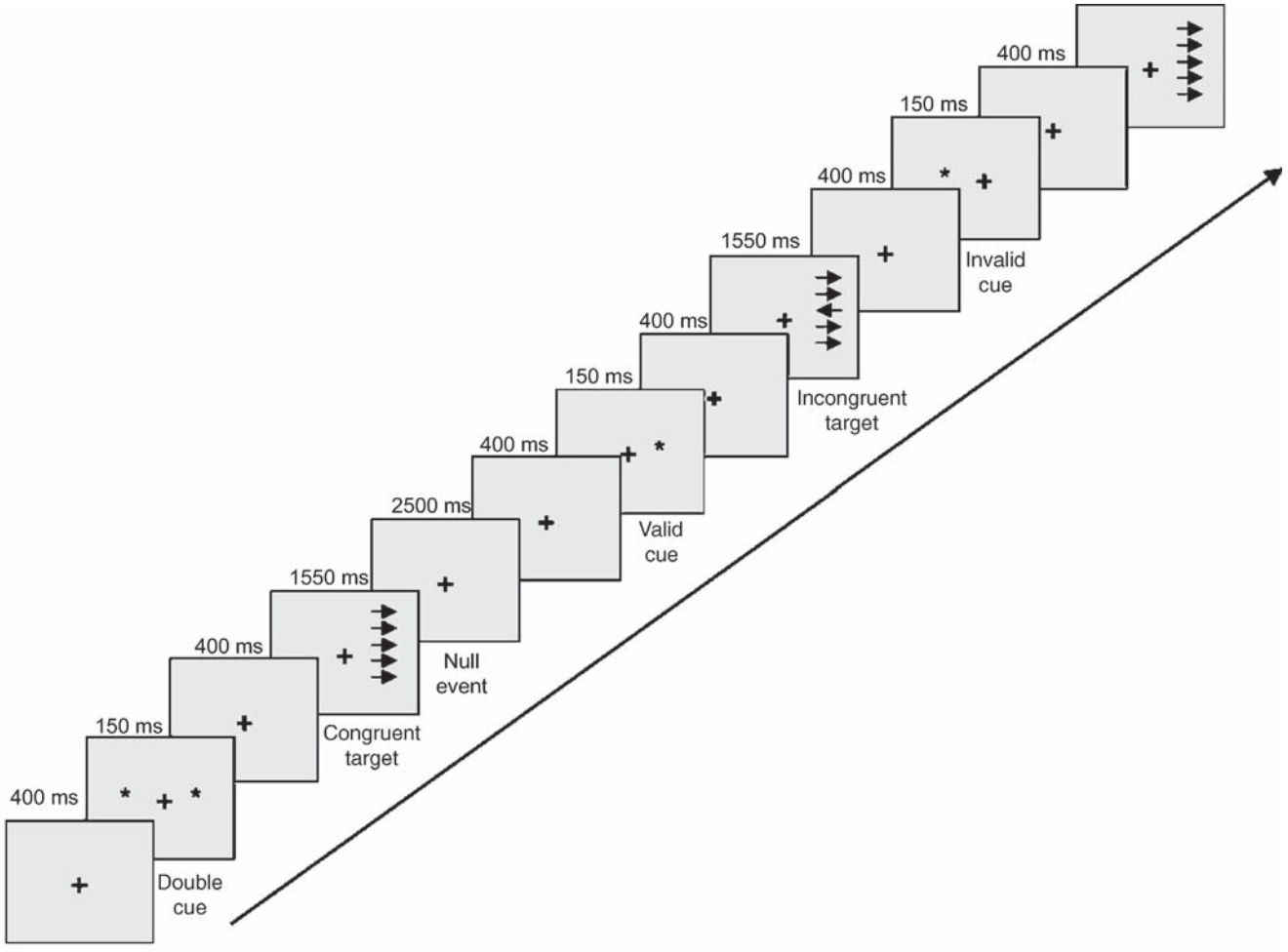

FIGURE 15.32 Experimental paradigm: modified version of the Attentional Network Task (Fan *et al*., 2002). This figure illustrates the time course of the four different cue and the two target conditions. *Source*: Konrad *et al*., 2005.

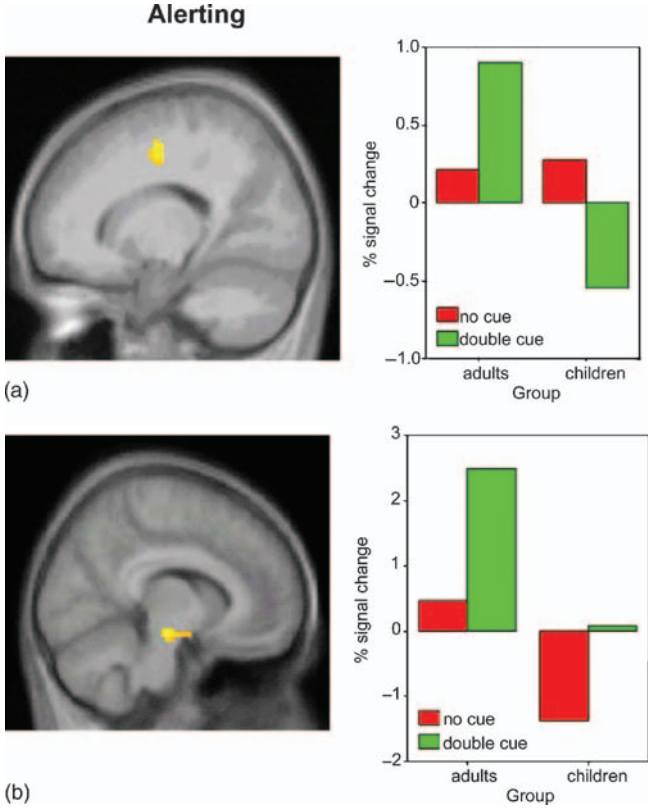

FIGURE 15.33 Alerting results. Differential activation of adults and children as identified in a two-sample test for the alerting condition (thresholded at $p_{svc} < 0.05$, extend threshold 5 voxel, shown on averaged group T1 image). (a) Increased activation in the right cingulated gyrus in adults compared to children. (b) Increased brainstem activity in adults compared to children. Plots of the percent BOLD signal change are shown separately for both groups as a function of trial type (pooled over congruent and incongruent targets) for the respective activation maximum. *Source*: Konrad *et al.*, 2005.

3 executive control of attentional processes (Posner and Peterson, 1990).

For example, consider the 6-year-old child in a first grade classroom. In order to cope with the complex environment with many sensory inputs competing for his attention, he must first be ready and in an alert state. Next, he must be flexible in changing his attentional focus to orient to new sensory inputs, for example, or to reorient to relevant information when required. Last, he must have a means for controlling these attentional resources.

These processes have been the focus of much study in adults. In adults, brain areas for alerting processes are located in frontal and parietal regions in the right hemisphere (Witte and Marrocco, 1997). Brain areas for orienting are located in the right hemisphere temporo-parietal junction and the inferior frontal gyrus (Corbetta *et al.*, 2000). Brain areas for executive control include the anterior cingulate and lateral prefrontal cortex (Marrocco and Davidson, 1998). Konrad and colleagues (Konrad *et al.*, 2005) used these brain areas that have been demonstrated to be active in adults during performance of the ANT as regions of interest in an fMRI study of 16 boys, aged 8–12 years, and 16 male adults.

Results for the alerting portion of the protocol are presented in Figure 15.33. Children did not show adult-like activation patterns in the predefined regions of interest. The key activation differences between adults and children were in the right frontal cingulate gyrus (Figure 15.33, upper panel) and the midbrain (Figure 15.33, lower panel). The authors suggested that these differing patterns of activation are due to modulation by 'top-down' mechanisms used in the task by the adults that may not be fully established in children in the age range of 8–12 years.

Results for the reorienting portion of the protocol showed a typical pattern of right hemisphere activation for the adults, while the children showed a more diffuse and broader distribution of activation during reorienting. These differences can be summarized as increased activation in the right side temporo-parietal junction in adults versus children (Figure 15.34(a)); stronger activation in the putamen and insula in children versus adults (Figure 15.34(b)); and increased activation in the superior frontal gyrus in children versus adults (Figure 15.34(c)). These findings may represent the recruitment of brain regions for performing the tasks due to immature cognitive control mechanisms in young children.

The results of the executive attention portion of the protocol showed increased activation in the superior parietal cortex and inferior frontal gyrus in adults versus children (Figure 15.35(a,b)), and increased activation in the superior temporal gyrus and superior frontal gyrus in children versus adults (Figure 15.35(c,d)).

Cumulatively the results of the study by Konrad and colleagues show a strikingly differing pattern of brain activation for children versus adults when performing attentional tasks. While these results must be treated with caution until more studies can be completed using similar tasks and brain measures, the results of Konrad and colleagues provide evidence for immature frontal-parietal networks in cognitive control tasks, a finding similar to the results reported by Casey and colleagues (reviewed in Casey *et al.*, 2005).

A general conclusion from these fMRI studies of cognitive control in children provides evidence for attentional systems that are functional but immature

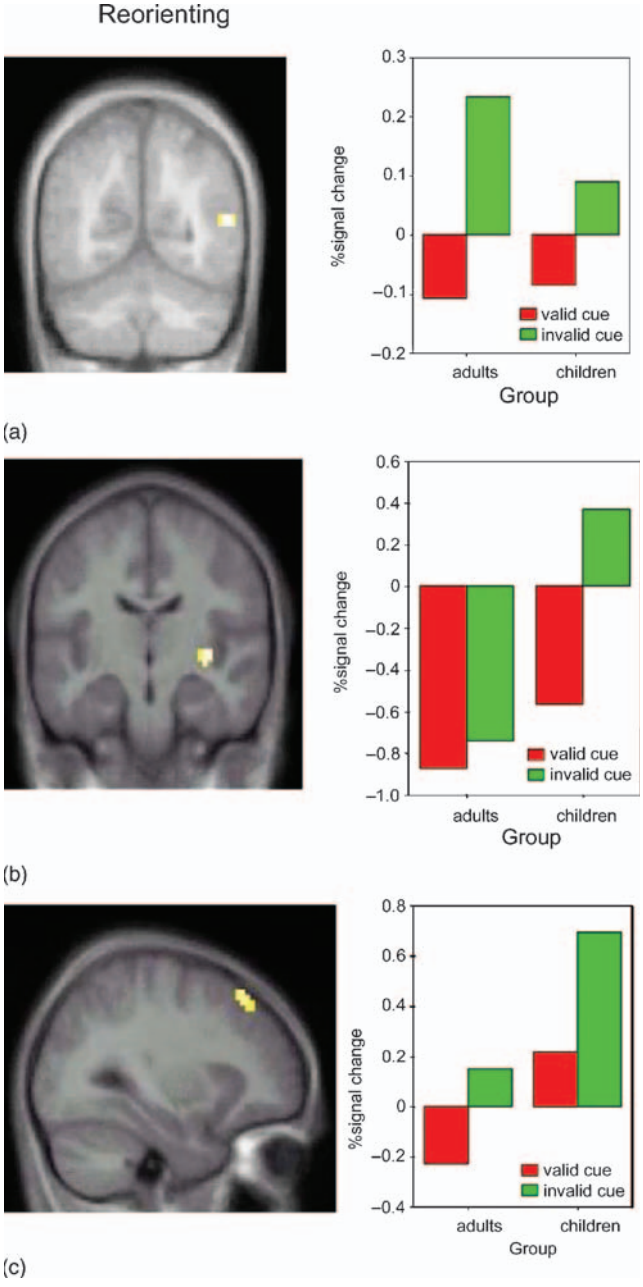

FIGURE 15.34 Differential activation of adults and children as identified in a two-sample test for the reorienting condition (thresholded at $p_{svc} < 0.05$ or $p < 0.1$ corrected for multiple comparisons for whole-brain analyses, extend threshold 5 voxel, shown on averaged group T1 image). (a) Increased activation in the right-sided temporo-parietal junction in adults compared to children. (b) Stronger activation in the putamen and insula in children compared to adults. (c) Increased activation in the superior frontal gyrus in children compared to adults. Plots of the percent BOLD signal change are shown separately for both groups as a function of trial type (pooled over congruent and incongruent targets) for the activation maximum. *Source*: Konrad *et al.*, 2005.

in children as compared to adults. Children show a pattern of activation that is more diffuse and encompasses a wider area of brain regions than those active in adults. These findings may reflect the immature nature of the systems during childhood, which may become more focal and specialized with development and experience.

Future work in the investigation of cognitive control and development of PFC in children will need to take into account many other aspects of the prolonged developmental path of the frontal regions and the correspondence to behavior. Some areas of future research may include investigating gender differences in cognitive control functions and related brain activation patterns. You may have noticed that most of the tasks detailed in this section included visual presentation of task items. More work is needed to evaluate the frontal lobe networks that mediate auditory attentional control as well as those that subserve tasks that require integration of multimodal (e.g. visual + auditory) information in task performance.

4.2.3 The social brain: face perception in childhood

Human face perception has been the focus of many neuroimaging and behavioral investigations in adults, in infants, and throughout childhood and adolescence. Why is this area of research important to the field of cognitive neuroscience? Investigating brain regions that may be specialized for perception of our species-specific faces may shed light on the nature versus nurture debate. Are we predisposed to attend to, focus on, and interpret cues in faces? Or does our vast experience with faces provide the information processing abilities that are not specific to faces, but rather utilizes visual object perception networks? Studying face processing during development may help us determine how genetic predisposition interacts with experience.

Recall that, in infants, investigations of face processing used ERP measures and, in particular, evaluated the modulation of the N170 component in response to faces as compared to other visual objects. Results from these studies as well as studies using other imaging techniques (MEG, fMRI) provide converging evidence that face processing is less specialized in young children (5–10 years) as compared to older children (11–14 years), with more diffuse and less focal brain activity for faces (Gathers *et al.*, 2004; Aylward *et al.*, 2005; Kyllainen *et al.*, 2006). Also, older children show more bilateral fusiform face area activation for faces as compared to houses than younger children, and the pattern of activation correlates with age (Aylward

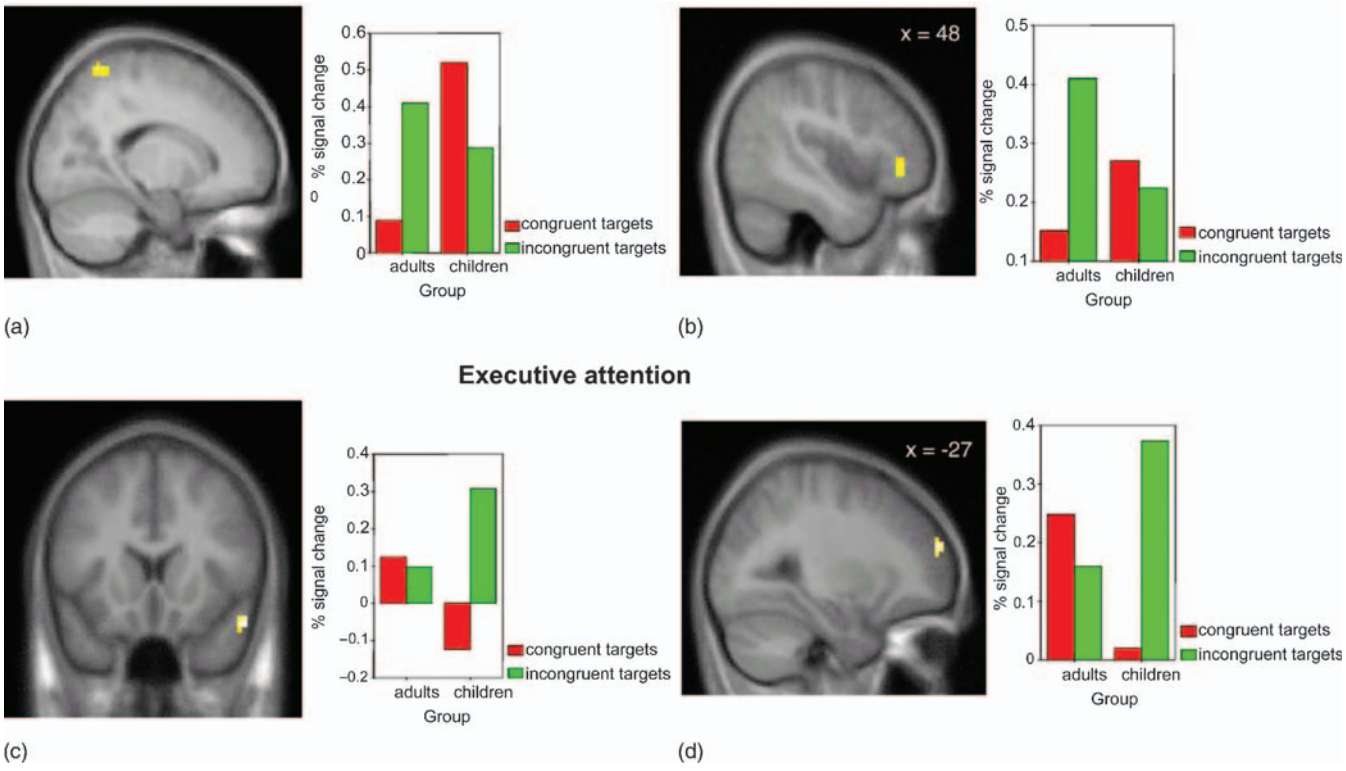

FIGURE 15.35 Differential activation of adults and children as identified in a two-sample test for the executive control condition (thresholded at $p_{svc} < 0.05$ or $p < 0.1$ corrected for multiple comparisons for whole-brain analyses, extend threshold 5 voxel, shown on averaged group T1 image). (a) Increased activation in the superior parietal cortex and (b) inferior frontal gyrus in adults compared to children. (c) Increased activation in the superior temporal gyrus and (d) superior frontal gyrus in children compared to adults. Plots of the percent BOLD signal change are shown separately for both groups as a function of target type (pooled over cueing conditions) for the activation maximum. *Source*: Konrad *et al.*, 2005.

et al., 2005). Nevertheless, these studies indicate that, while older children show more focal activation than younger children, they do not show adult-like patterns of response, indicating that face perception is a slow-to-mature process.

Most of these studies use faces with neutral or happy expressions; however, they leave open the question of how children perceive emotional information in faces. Understanding emotional cues in facial expressions is a vital aspect of social cognition in humans. The study of face processing of emotional cues is complex, however, and not well understood in adults let alone in developing children. Here, we highlight two recent studies of emotional cues in faces with children: one study uses fMRI to elucidate brain regions employed in decoding emotional face cues and the second utilizes the EEG N170 component to investigate the time course of emotional cues in face processing. It is important to note that the study of the developmental path of emotional cues in face processing is in its early stages: while these studies provide some useful early data for understanding how these processes develop and mature, much more work is needed before we can claim to understand fully the intricacies of human face perception.

Batty and Taylor (2006) investigated the N170 response for faces showing six different emotions (happiness, surprise, sadness, fear, anger, and disgust) as well as a neutral face in a large sample (82) of children between the ages of 4 and 15 years. Batty and Taylor reported that only the oldest group of children (14–15 years) showed N170 patterns of response that were similar to adults. And, even in this group, the N170 response did not appear to be adult-like in discriminating between emotional cues. They suggested that interpreting complex emotional information in human faces was a slow-to-mature process that was not fully realized even in middle teenage years.

A related study was conducted by Lobaugh and colleagues (Lobaugh *et al.*, 2006) using fMRI and the same eight emotional categories. In this study, the children were 10–12 years old. Lobaugh and colleagues used a gender decision task for investigating emotional cues in faces: the children were asked to decide if the face

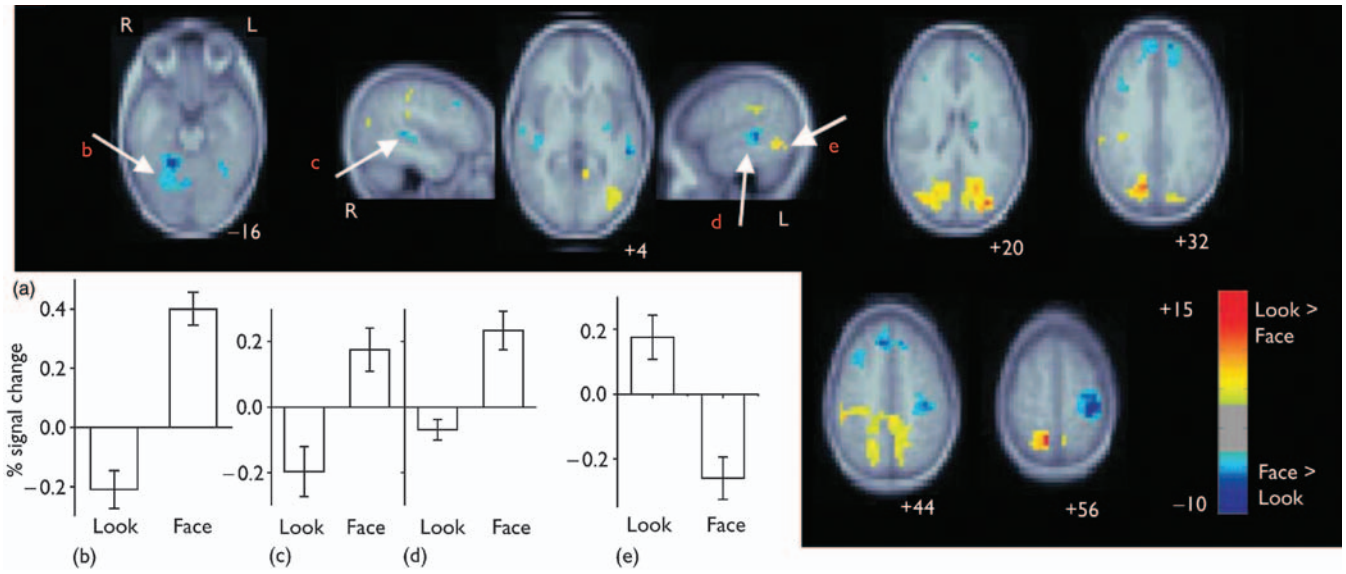

FIGURE 15.36 Face versus look results. (a) Regions in blue showed more activity on face trials than look trials. The response was reversed for regions in yellow/red. Arrows (b–e) highlight peak clusters. Mean percentage change (±SEM) in peak voxel response across the block is shown for the selected clusters. (b) A large expanse of right fusiform/parahippocampal gyrus (20/40/16) was more active in the face task. (c and d) Bilateral superior temporal gyrus (c: 48/32/+4, d: +44/32/+8). (e) Posterior temporal gyrus (44/52/4) showed decreased activity to faces. *Source*: Lobaugh *et al.*, 2006.

was male or female. In this way, Lobaugh and colleagues attempted to understand the neural substrates of implicit recognition of emotional cues during face processing. First, Lobaugh and colleagues evaluated brain areas that were differentially responsive to faces versus a looking condition. These are shown in Figure 15.36. These areas were right fusiform/parahippocampal gyrus, which were more active in the face task, and bilateral superior temporal gyrus and posterior temporal gyrus, which showed decreased activity in the face task.

A second key finding was that brain activation to negative emotions (disgust, fear) was stronger than responses to positive (happiness) or neutral emotions (Figure 15.37). The strongest responses were to faces with expressions of fear. The authors interpreted these findings to indicate that functional emotional networks are established by age 10.

What do the findings of the work of Batty and Taylor and Lobaugh and colleagues tell us about how children understand complex emotional cues in faces? It is important to note that the brain measures used by the two studies (ERP study of the latency and amplitude of the N170 component versus fMRI study of hemodynamic changes) are quite different in just what brain responses they are able to measure. Next, one study (Batty and Taylor, 2006) had a large sample (82) of children across a wide range of ages (4–15 years), while the other had a small sample (10) of children in a narrow age range (10–12 years). The differing tasks and techniques used in these studies make an interpretation of the findings problematic in spite of the fact that the two studies investigated very similar processes, emotional cues in faces.

The investigations presented here provide early evidence for differing patterns of brain response in childhood when processing emotional cues in faces. Many more studies are needed in order to for us to understand fully the brain area and developmental path of emotional cue processing in face perception. Some important aspects of the future studies may entail determining if boys and girls process emotional cues in a similar way and assessing if children pay more attention to certain aspects of faces (such as eyes) as compared to adults.

What have we learned about the development of language, executive function and social cognition in childhood and adolescence? One central finding from a variety of data sources (histological, pathological, neuroimaging) is that the cortical regions subserving these high order cognitive functions have a prolonged developmental path extending to mid- to late adolescence. We have a wealth of behavioral data showing a similar pattern in tasks that tap more complex and higher order aspects of these cognitive functions, with task performance not reaching adult-like levels until late adolescence. Putting these two bodies of information together in order to map brain development onto

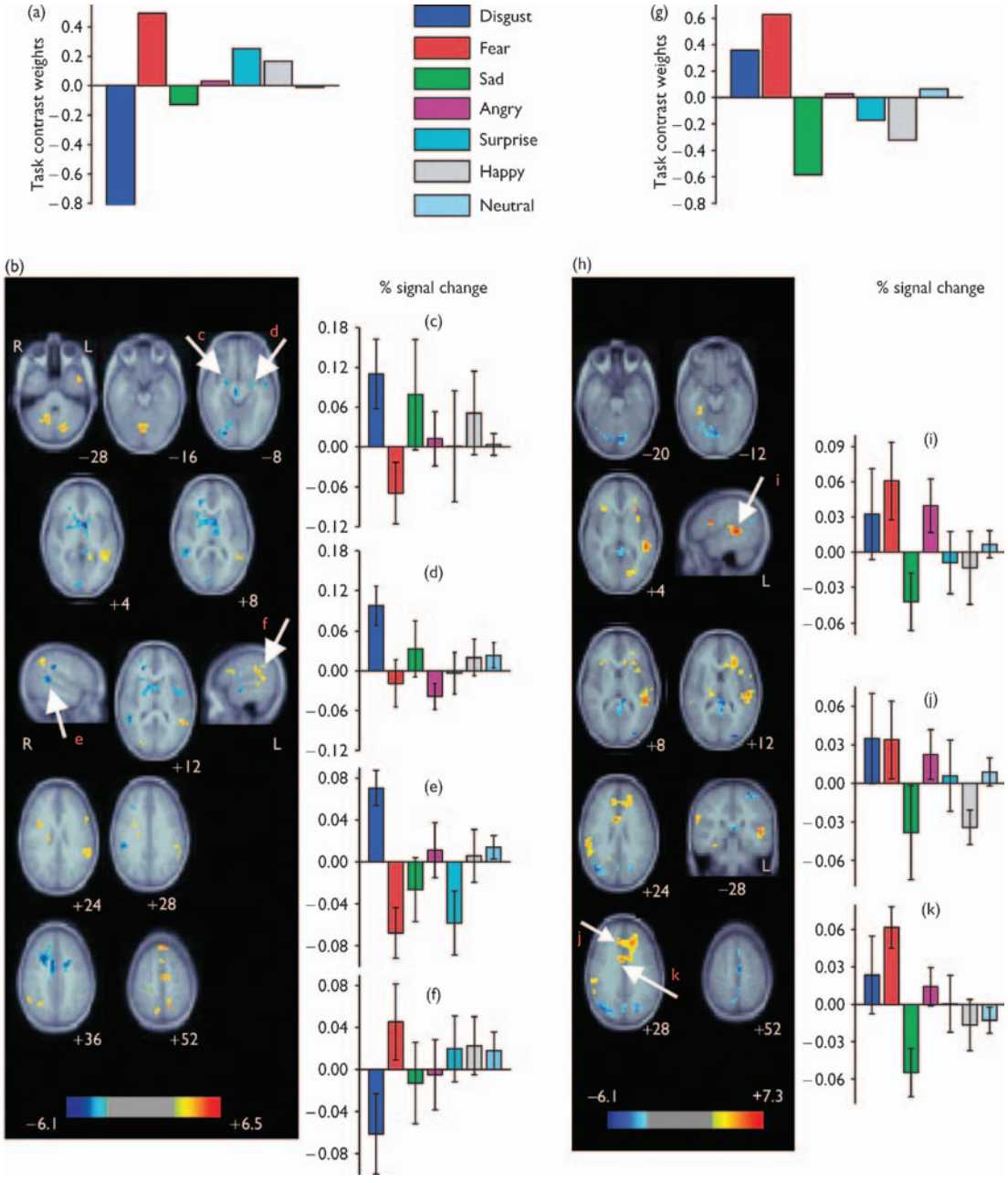

FIGURE 15.37 Emotional faces results. (a) Task contrasts for the first latent variable. The first pattern most strongly distinguished disgust (blue, negative task weight) from fear (red, positive task weight) and, to a smaller extent, from surprise (cyan) and happiness (gray). (b) Brain regions whose activity differentiated fear and disgust. Yellow/red: regions where the response to fear was greater than that to disgust; blue: regions where the response to disgust was larger than that to fear. (c–f) Location and mean percentage change (7 SEM) in peak voxels for selected clusters (mean of 8 TRs after trial onset). (c and d) Bilateral amygdala (c: +20/4/8; d: 24/4/8). (e) Right superior temporal gyrus (+48/40/+8). (f) Left superior temporal gyrus/inferior supramarginal gyrus (48/40/+20). (g) Task contrasts for the second latent variable. This pattern most strongly distinguished disgust and fear (blue and red, positive task weights) from sadness (green, negative task weight). Surprise (cyan) and happiness (gray) also differed from disgust and fear. (h) Brain regions whose activity most strongly differentiated fear and disgust from sadness. Yellow/red: regions where the response to disgust and fear was greater than that to sadness; blue: regions where the response to sad faces was larger than that to disgust and fear. (i–k) Mean percentage change in peak voxels (7 SEM) for selected clusters. (i) Left superior temporal gyrus (44/28/+8). (j and k) Anterior cingulate (j: +12/+36/+24, BA 32; k: +8/+8/+28, BA 24). Color bars indicate the magnitude of the voxel stability. Left is on the right of the image. *Source*: Lobaugh *et al*., 2006.

cognitive function remains a challenge for the developmental cognitive neuroscientist.

While we have made significant headway, as data presented in this chapter demonstrate, there are many complexities in each of these areas of cognition that remain undiscovered. While we have a general notion of how language emerges in young children, the cortical mapping of complex language systems is still being worked out in adults, with less known about the patterns of emergent language. Similarly, the field continues to discover how PFC subserves aspects of tasks tapping attentional, planning, and working memory systems. The relation of these networks with ability or specific task demands is still unresolved in adults and remains to be elucidated in children. Face perception and the integration of emotional, linguistic, and pragmatic cues faces into social cognition knowledge is also an ongoing field of investigation in adults, with less known about the emergent patterns and trading relations among these many factors in understanding human social behavior.

An important direction in the field of developmental cognitive neuroscience is to combine methodologies – for example, fMRI with EEG – with behavioral measures in order to provide converging evidence across methodologies and measures regarding aspects of higher order cognitive function. Combining fMRI with EEG, for example, can provide high resolution spatial information regarding brain activations coupled with high resolution of the time course of that activation. Another important direction in the field is to conduct longitudinal studies in order to track the development over time of individual children. In this way, early 'baseline' measures can be taken and then the development and change in these measures may be assessed at specific intervals. Finally, new experimental design approaches with young infants are demonstrating that babies know and understand a lot more about the world around them than we previously thought. New advances in measuring infant cognition and mapping the relevant brain activity will provide important insights into the developmental changes occurring in the first year of life.

5.0 EARLY BRAIN DAMAGE AND DEVELOPMENTAL PLASTICITY

We mentioned, above, the importance of longitudinal studies for tracking individual progress and outcomes throughout development. This type of study is especially important when assessing the long-term outcome of early (perinatal) brain injury. We have seen in earlier chapters that, in adults, brain damage due to stroke, disease, or traumatic accident typically leads to deficits in aspects of cognition that are fairly severe, with complete recovery of function unlikely. What happens when brain damage occurs near birth? This question has an important bearing on the nature versus nurture debate. Consider the hypothesis that some brain systems, such as language, have a strong genetic predisposition for their development in specified regions of the brain. If there is early insult to those pre-specified regions, will the infant develop language in a typical fashion? Or will language develop in an aberrant fashion due to the early and unrecoverable damage to those brain regions? Alternatively, if experience plays the dominant role in the development of brain regions that become tuned for language function, will the infant develop language in a typical fashion in spite of the early brain damage?

The effects of perinatal brain damage have been extensively investigated in animal studies in the field of neurobiology. The effects of early brain damage and the impact on later cognitive development have been far less studied in humans. One reason for this is that a single, unilateral (in one hemisphere only) pre- or perinatal brain insult is relatively rare. Typically, instances of early brain insult are more global in nature and combine with other neurological complications (Figure 15.38, left panel). In these cases of larger scale damage coupled with other traumatic events, it is difficult to compare cognitive development to children without this early damage and trauma. In cases where the perinatal damage is limited to a circumscribed region (Figure 15.38, center and right panels), the long-term effects are typically milder. These are the types of cases that we will focus on in this section: early, focal, unilateral brain insult.

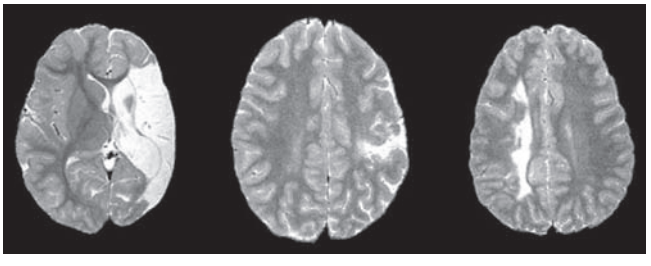

FIGURE 15.38 Large scale and smaller scale perinatal brain damage. Structural MRI scans in the axial plane from three children with perinatal brain damage, illustrating different patterns of injury. *Left*: A large unilateral lesion involving most of one cerebral hemisphere. *Middle*: A small lesion confined to one cerebral lobe. *Right*: A deep lesion involving subcortical regions. *Source*: Stiles *et al.*, 2005.

While we are just beginning to understand the complexities of early insult on later cognitive growth in humans, a series of longitudinal studies by Stiles and colleagues (2005) shed some light on the long-term effects of perinatal insult and we highlight some results here (for a review, see Stiles *et al*., 2005). The San Diego Longitudinal Project (Stiles *et al*., 2002) is the largest U.S. investigation of the long-term effects of perinatal brain damage. Stiles and colleagues have followed the cognitive development of several hundred children with perinatal brain damage since 1989.

Much of the focus of the investigations by Stiles and colleagues in the San Diego Longitudinal Project has been on language development in children with perinatal brain damage. One key finding is that, while in adults, focal brain damage (typically through lesions due to stroke) in language centers results in long-lasting deficits, this pattern is quite different with infants who suffer perinatal brain damage. While there is typically delay in early linguistic milestones, such as onset of word comprehension at 9–12 months and word production at 12–15 months, by the age of 5 years, these children have largely 'caught up' in linguistic abilities. The important finding, however, is that when tested carefully there remain some underlying deficits even at the age of 5, especially in complex sentence structures (Reilly *et al*., 2004). These children with early brain damage do ultimately achieve language competence, but the evidence provided by the longitudinal studies by Stiles and colleagues (reviewed in Stiles *et al*., 2005) indicate that their language proficiency is in the lower than normal range. Thus, while the children do acquire many skills and proficiencies with respect to language, there remain throughout childhood, adolescence, and presumably adulthood, some key deficits due to the very early damage to important brain regions for language acquisition and processing.

Another aspect of cognition that has been the focus of study by the San Diego Longitudinal Project has been spatial cognition. Spatial cognition and the effects produced by adult acquired brain damage have been the target of many neuropsychological and neuroimaging investigations. The central findings have been that there is a hemisphere asymmetry in the decoding of visual patterns, with the left hemisphere biased for extracting feature (local) information and the right hemisphere biased for extracting configuration (global) information (Figure 15.39).

Functional MRI studies of typically developing adolescents show that they demonstrate a similar hemisphere asymmetry, with greater right hemisphere occipital-temporal activation for global processing and

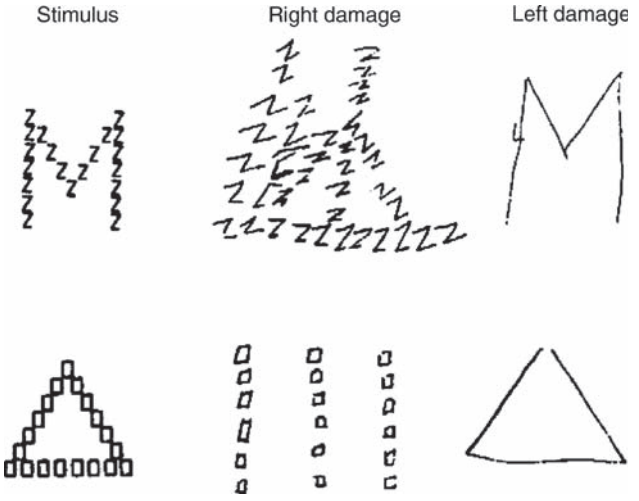

FIGURE 15.39 Global versus local: examples of visuospatial deficits. Examples of memory reproductions of hierarchical form stimuli by adult stroke patients with either right or left hemisphere injury. (Adapted, with permission, from Delis *et al*., 1986.) The sample stimulus to be copied is shown on the left side of the figure. Center of the figure: patients with right hemisphere damage typically produce the local (detailed) aspects of the stimulus but omit the global (overall) aspects of the stimulus: in this case, the 'M' or triangle shape of the stimulus. Right side of the figure: patients with left hemisphere damage typically produce the global aspects of the stimulus but omit the local aspects of the stimulus. *Source*: Stiles *et al*., 2005.

greater left hemisphere occipital-temporal activation for local processing (Figure 15.40). In stark contrast, a 15-year-old adolescent who had suffered right hemisphere perinatal brain damage showed stronger activation for both global and local processing in the left (undamaged) hemisphere (Figure 15.40) and a 13-year-old adolescent who had suffered left hemisphere perinatal brain damage showed stronger activation for both global and local processing in the right (undamaged) hemisphere (Figure 15.40). Thus, the fMRI data for the two adolescents who suffered perinatal brain damage provide evidence for long-lasting damage to spatial cognition mechanisms. However, they also provide intriguing evidence for a brain system that is highly flexible, with recruitment of neural territory in the undamaged hemisphere for spatial cognition functions.

What have we learned about the long-term effects of early brain damage in the longitudinal studies of Stiles and colleagues? And how do they inform us about the complex and highly interactive roles of nature and nurture in human development? While these efforts are still in the early stages, results to date indicate that early brain damage results in long-term, though typically somewhat subtle, deficits. A second important finding is that despite the early insults and

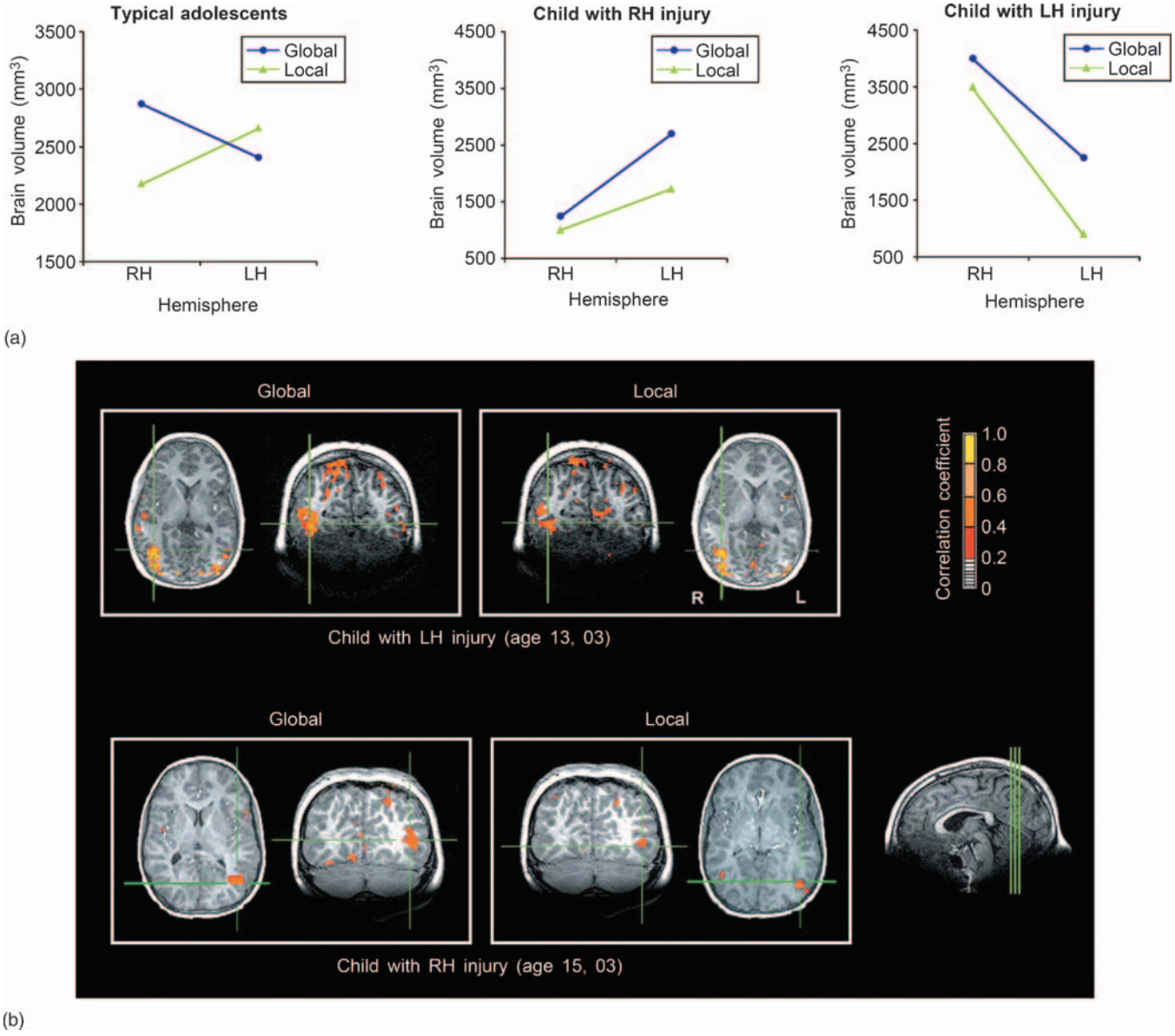

FIGURE 15.40 Global and local processing in the brain. Functional MRI activation data from two teenagers with prenatal focal brain injury on a hierarchical form-processing task, compared with data from typical adolescents. Each child participated in separate imaging runs, where they were asked to attend to either the global or the local level of the stimulus pattern. Unlike typical controls, who show different patterns of lateralization for global and local processing, the two children with lesions showed activation largely confined to the uninjured hemisphere. Activation images for the two children with perinatal brain injury are shown. *Source*: Adapted from Stiles *et al.*, 2005, with permission.

the delays that they typically produce in cognitive development, the children mature and acquire higher cognitive function, although sometimes at the lower than normal level. Cumulatively, these findings provide evidence that there are some brain systems that have long-term impairments when damaged, even when the damage occurs at or near birth. This provides some support that some systems have a level of genetic predisposition and can suffer long-term harm when disrupted. On a brighter note, these findings provide evidence for significant amounts of early brain plasticity so that the cognitive functions that suffer early damage develop in an alternative manner.

6.0 SUMMARY

In this chapter, we have tracked the stages of human development from early embryo to infant to adolescent. While the field of developmental cognitive

neuroscience is still a very young one, nevertheless, the findings presented in this chapter demonstrate the answers to important questions about human brain development and the correspondence to cognition. An overarching topic of much debate in the field of human development is the role of nature versus nurture. From the data presented here, you see that at each stage of human development there are important genetic effects and biological constraints at work in the unfolding of the human brain and mind. Similarly, at each state there are critical effects of the surrounding environment, whether at the level of the cell, the system, or the brain.

The advent of new techniques for non-invasively studying human development has provided the means to address new questions about cognitive development, such as what does a baby know before birth? Does an infant understand the grammar of language? How does the sense of self develop in an infant, a child? What are the long-term effects of focal brain damage? These and other questions will be addressed in future studies investigating the unfolding complex pattern of human brain development and its relation to cognition.

7.0 CHAPTER REVIEW

7.1 Study questions

1 In what ways have neuroimaging techniques changed the way infant and child development is investigated?
2 What does the term 'bidirectional influences' refer to in human development? Why is it an important concept?
3 Provide an example of a nature and nurture interaction that occurs before birth (prenatally).
4 What are some effects of maternal use of alcohol, tobacco, and marijuana on her unborn child?
5 What brain regions develop and mature early in childhood? What regions develop later in childhood?
6 The development of object permanence in infants has been the focus of much study. Describe an experiment for investigating object permanence and possible results for:
   a a 6-month-old infant.
   b a 12-month-old infant.

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The human brain has been creative ever since the emergence of behaviorally modern people. Lascaux cave painting, estimated to be 16 000 years old. *Source*: http://en.wikipedia.org/wiki/Lascaux

CHAPTER

16

The genes and molecules of cognition

OUTLINE

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

1.0 INTRODUCTION

What do chocolate candy and the sting of a bee have in common? Both act by way of signaling molecules between brain cells. Chocolate tastes good and insect bites itch – both are brain responses. A great variety of everyday molecules shape our experiences, including coffee, aspirin, vitamins, beer, oils and fats, medicines, sugar, nicotine, and diesel fumes. Insect bites and snake poisons involve *neurotoxins*, chemicals that interfere with neural transmission. Eggs provide choline, which is used to make the neurotransmitter *acetylcholine*, a molecule needed to stay awake. Milk contains *tryptophan*, the first step for producing *serotonin*, which is why a glass of warm milk at night may promote sleep. Coffee, tea, and chocolate all have some caffeine, which inhibits the neurotransmitter *adenosine* by competing for its receptors (Figure 16.1). Neurotransmitters are ever-present players in everyday life.

Ordinary food and drink is full of neuroactive molecules, including sugars (glucose being the food of the brain), choline (from eggs), and whole proteins (from milk, meat, eggs, nuts, and seeds). *Calcium* is utilized for a huge variety of cell functions, including neural transmission. Ultimately, we get all those building blocks from the food we eat and the air we breathe.

All living things are made of carbon chains, which act as Lego bricks that can make up an endless variety of buildings and figures. The carbon chains utilize hydrogen, nitrogen, oxygen, calcium, magnesium, and trace minerals. Proteins are long chains of amino acids, carbon-hydrogen chains using the NH_2 and COOH fractions. All amino acids can be made from whole protein foods, which provide the twelve 'essential' amino acids.

FIGURE 16.1 Coffee, tea, or adenosine? The three-dimensional shape of molecules determines many of their effects. Caffeine and theophylline both resemble the neurotransmitter *adenosine* in their chemical shapes, and by blocking the adenosine receptor they increase alertness. Adenosine is also part of the basic biological energy molecule ATP (adenosine triphosphate); neurotransmitters often make use of existing biomolecules.

1.1 Basic life molecules are also used for neuronal signaling

Scientists often seem to talk in their own code, and the vocabulary of brain molecules can seem overwhelming. To remember the words it helps to look for roots. The word *cannabinoid* (ka-NA-bin-oid) comes from the Latin name for the psychoactive molecules of the hemp plant, *Cannabis sativa,* with the ending-*oid* to express the fact that those molecules are 'like' the cannabis we find in plants. *Endo-cannabinoids* are *endogenous* cannabis-like molecules, produced inside the body itself.

Brain molecules often are named after their first known role in the body. Thus *serotonin* was first described as a substance that raised blood pressure (the *tonus* of the *serum*; pronounced SE-ro-TOE-nin). The ending '-in' or '-ine' indicates a protein, as in the word 'protein' itself. Though serotonin does raise blood pressure when it enters the bloodstream, in the brain it helps to run the sleep-waking cycle, along with regulating mood and dreams. But it still keeps its original name, giving us a useful trick to help remember it. Like street signs, chemical names commonly carry their own history.

Memory techniques can be very efficient. To remember the words you can look for similar ones that you already know, even if the association is imaginary. (If 'serotonin' sounds like 'cherry toenails' to you, that will work fine, especially if you can visualize it.) For spatial facts like the landscape of the brain and the layout of synapses, nothing works as well as drawing and coloring. Learning is an active and interactive process, and the more you can actually do with the terms in this chapter, the better you will remember them. If you can actively reconstruct the main points in your own words, you will have a solid foundation of understanding.

The brain itself supplies some simplifying rules of thumb. One is that life constantly uses the same molecules in different ways. Most of the molecules we discuss in this chapter exist across many animal species, from the fruit fly and the snail-like *Aplysia* to human beings. Molecules that are involved in energy metabolism and heredity, basic life functions, are constantly reutilized for neuronal signaling. All animal cells maintain a voltage difference across their cell membranes, but only neurons use that voltage to send an action potential (spike) down the axon. All cells use ATP to store energy, and ATP is also reutilized as a neurotransmitter in its own right. Glutamate is a basic amino acid in all cells, but it is also the most common

excitatory neurotransmitter in the brain. There are numerous other examples. The fact that nature reuses its basic molecules to run nervous systems helps in learning the vocabulary.

Simpler animals are intensively studied as model organisms to work out the most basic biological events. Synapses are tiny and complex, and historically required invasive surgery to study, not something that is ethically permitted in humans. They were therefore first studied in simpler animal models and even in laboratory cultures. Those tools continue to reveal new facts.

Animal biology shows a number of highly conserved genes, molecules, and nerve cells. By *conserved*, we mean that they are found across many species. For example, we share five major classes of neurotransmitters with insects. That does not reduce human beings to fruit flies, but it makes the fruit fly useful as a model to study. The electrical brain activity of a moving fruit fly actually resembles the EEG of the waking brain in humans. Such similarities across hundreds of millions of years of divergent evolution are part of the fun of learning the biology of brainy creatures.

Looking closer to home, other mammals share earlier evolutionary structures with us. The neocortex, and especially the frontal lobes, have grown on those shared foundations. The brain contains its own evolutionary history.

Molecules work at the most powerful level of biological control. Genes are encoded in molecules, the nearly two meters of DNA in each cell, which is *transcribed* into messenger RNAs, which are then *translated* into target proteins (Figure 16.2).

The brain cannot work without a constant flow of oxygen and glucose, about a quarter of the body's energy supply. It also needs regular protein, vitamins, minerals, oils, and fats – the last are required to build cell membranes and the myelin sheath surrounding neurons. Some oils have been shown to raise mood (the omega 3 oils). Molecules like *dopamine* and *acetylcholine* are essential for pleasure, for staying awake, and for immediate memory.

The molecular machinery of the brain can seem overwhelming. This chapter will cover the basics. In spite of the dizzying dance of molecules we can still think of all the steps as either increasing or decreasing the function of a specific target chemical. A dopamine *agonist* is anything that increases the functions of dopamine. Thus the famous Parkinson's drug, L-dopa, is an ingredient for making dopamine, and therefore can act as a dopamine agonist. SSRI antidepressants – selective serotonin reuptake inhibitors – *reduce the reuptake* (recycling) of serotonin. If you don't recycle a molecule you get more of it. So the overall effect of SSRIs is also to be an *agonist* of serotonin. Simply counting the ups and downs of each step will give you the overall story. It may be helpful to write down small up and down arrows for each step (↑ and ↓) to keep track of the whole series of events.

On the other side of agonists, *antagonists* lower the effects of a neural messenger. A prominent example is the drug naloxone, which is used to reverse the deadly effects of an opiate overdose. Naloxone competes for opiate receptor slots, and thereby reduces the effects of toxic quantities of opiates. Like other neural molecules, opiates have important uses as well as risks.

In sum, no matter how complicated the molecular dance becomes, a psychoactive chemical ends up either increasing or decreasing the effects of some brain molecule.

This chapter explores the molecules of cognition. We want to know how molecules help to carry brain signals and perform the computations that make the human mind possible.

1.2 Life uses enzymes

Living organisms operate within very narrow limits of temperature, pressure, and acidity. Humans learned to cook their food about 10 000 years ago, and to make high-temperature steel about two centuries ago, in order to make most of our technology. But the body cannot tolerate extremes of heat, pressure, or acidity; that would kill us. Instead, life uses *enzyme* chemistry,

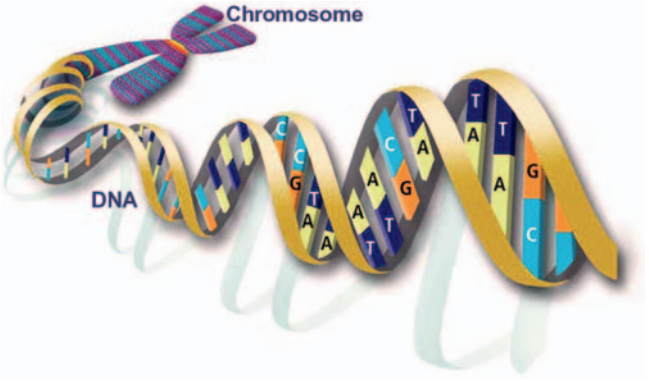

FIGURE 16.2 DNA and the enzymatic chemistry of life. In a broad sense all biochemical players are controlled by enzymes, including DNA itself. Enzymes enable chemical reactions by locking into substrate molecules, like a key in a lock. They can cleave, transport, and release other molecules, very much like nanomachines. Enzymatic reactions are more efficient than simple chemical reactions, and have major amplifying effects. DNA is both a code-preserver and a source of endless molecular amplification. *Source*: National Institute of General Medical Sciences, 2009.

making constant use of molecular nanomachines that speed along a second-by-second flow of chemical reactions. All brain chemicals act enzymatically.

The easiest way to think about enzymes is with the traditional 'lock and key' analogy; it is the three-dimensional shape of the molecules that allows them to lock into each other, transport molecules, change their shapes, or use them to send signals. *Vitamins* are essential enzymes to sustain life (from Latin, *vita*). Vitamin B12 and folic acid have important brain functions. Neurotransmission consists of enzyme-mediated signaling.

1.3 The same molecule may send different signals

The hemp plant does not produce *cannabis* to provide interesting experiences for humans. The coffee plant did not evolve to make coffee for your breakfast. Those molecules play different roles in their original plants than those they trigger in the brain.

But why are plant molecules so powerful for humans? Many useful drugs were first isolated from plants. Aspirin was derived from the bark of the willow tree. Curare comes from the arrow poison used by native people in Guyana, and played a major role in the discovery of one of the first known neurotransmitters, acetylcholine. Thousands of neuroactive molecules originally were derived from plants or other animals. The chemistry of life is highly *conserved*: the same molecule may act as an insecticide for a plant and as a neurochemical in animal brains.

A molecule may do different things even in the same animal. *Adrenalin* stimulates the body to prepare for 'fight or flight,' raising heart rate and breathing, and channeling blood to the lungs and outer muscles. Adrenalin is secreted from a gland on top of the kidneys (from Latin, *ad* = on top of, *renes* = kidney, *-in* = protein). In the brain it is called *epinephrine* using the same linguistic roots (Greek *epi* = on top of; *nephros* = kidney; *-ine* = protein).

In the brain norepinephrine is a major neuromodulator for wakefulness, different from the hormonal functions of adrenalin in the body. Similar molecules play different roles in different parts of the body.

1.4 The blood-brain barrier protects the internal milieu of the brain

One way for adrenalin to play one role in the body and another one in the brain is by compartmentalizing the distribution of the molecule, to ensure that when you get excited about a football game your brain doesn't overload with epinephrine. The *blood-brain barrier* was discovered shortly before 1900 when a chemist noticed that a blue dye injected in the brain did not spread to the body, or vice versa. Figure 16.3 shows some major features of the blood-brain barrier, which lines the blood vessels and ventricles of the brain.

The blood-brain barrier is a wall of separation between the body and its brain. It allows the brain to control its own internal milieu, separate from the bloodstream. The body itself is protected by layers of skin and muscle to separate it from surrounding chemicals. In the upshot, every cell in the brain is surrounded by many layers of barriers – the cell membrane itself, surrounding glial cells, the blood-brain barrier, the tissue barriers surrounding the brain, and the skin barriers to the outside world. Inside a brain cell, the nucleus constitutes yet another encapsulated organelle, and the nuclear chromosomes provide a protective medium to preserve the integrity of DNA. It's all biocontainers within biocontainers.

The brain and spinal cord have a private circulatory system separated from the bloodstream, called the *cerebrospinal fluid* (CSF). CSF serves to transport molecules and cells. A constant but controlled flow of chemical traffic flows to the brain by way of the CSF and the bloodstream.

Hormones are defined as signaling molecules carried to bodily organs via the bloodstream, while neural messengers lock on to receptors in the brain. But the brain is also richly vascularized with blood vessels, large and small. As we have seen, the fMRI method of brain recording picks up blood-oxygen-level-dependent (BOLD) changes in the magnetic signature of a brain region, when more blood is directed there to supply neurons and glial cells to run a specific task. The blood-brain barrier is a selective barrier, allowing oxygen and glucose to diffuse from the bloodstream, but blocking larger molecules like adrenaline.

1.5 Model organisms

Peas, insects, worms, and rats hold a special place of honor in science because they have long served as testbeds for studies that cannot be done in people (Figure 16.4). Each model organism rose to fame for biological discoveries that were difficult to observe elsewhere. Today the round worm *C. elegans* has come to the forefront, in part because we can identify every neuron in its body. Biological mechanisms are often highly

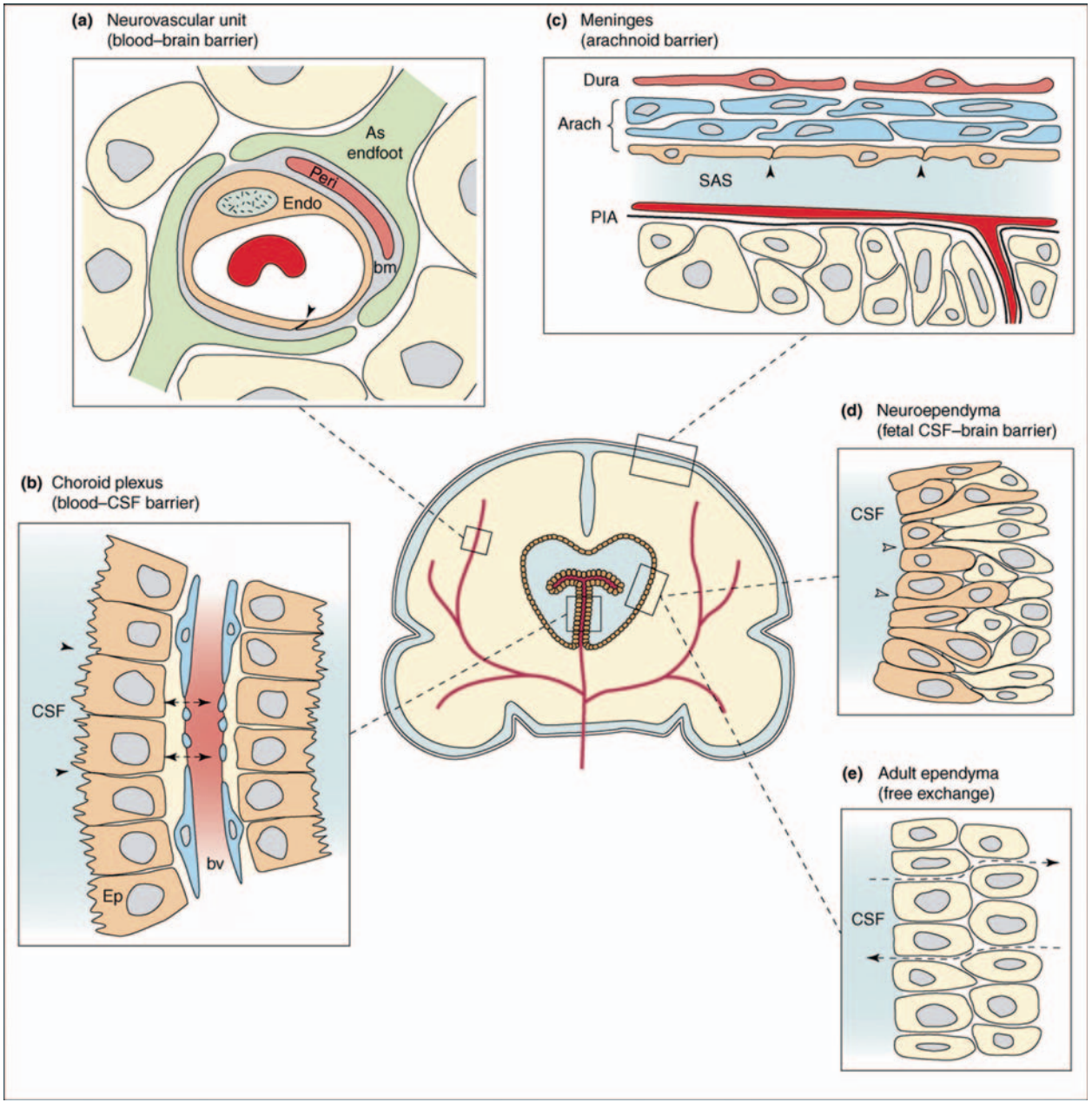

FIGURE 16.3 The brain is wrapped in protective layers of cells. The blood-brain barrier lines blood vessels in the brain as well as the cerebrospinal fluid vessels. The brain therefore has its own protected internal milieu, separate from the bloodstream, which in its turn is separate from other parts of the body and the environment. Large molecules, like proteins, are blocked unless they are specifically recognized and transported across the barrier. Similar cellular walls shield the fetal brain and the adult cranium from unwanted molecules. *Source*: Saunders *et al*., 2008.

conserved, so that we can learn about the human brain from the things it has in common with fruit flies and mice. Synaptic learning was first studied in the giant axon of the sea hare *Aplysia* because it was big enough to study under the light microscope. It is only today, decades later, that we are seeing direct evidence for synaptic learning in the human brain. In a sense, in biology we always start by looking in the wrong place. It is therefore vital to keep an open mind, to expect the unexpected.

The scientific study of peas and fruit flies began before 1900. Since the biogenetic revolution of the past few decades, numerous experiments have utilized 'gene knockout' and 'knockin' organisms. Using retroviruses it is possible to insert new genes into organisms, and to delete selected stretches of DNA. While

the mass of accumulated evidence is historic, there is still no substitute for clear thinking. Neurobiology is not a settled science – surprises keep happening.

Historically, acetylcholine (a-SEE-til-KO-leen, abbreviated ACh) was the first neurotransmitter studied. ACh was discovered in the neuromuscular synapse of experimental animals, outside of the central nervous system. The discovery of ACh had immense influence. For example, it was found to have *two* different receptors with quite different effects, a finding that alerted researchers to look for multiple receptors for other molecules. One of the ACh receptors was called *nicotinic* because it responded to nicotine, derived from tobacco. The second receptor was called *muscarinic*, because it was activated by the toxic ingredient of the poison mushroom, *Muscarina amanita.*

ACh itself has two different guises: outside of the central nervous system it is a neuromuscular transmitter, but in the brain it is a major neuromodulator, with effects that are quite different from its peripheral role. Our understanding of acetylcholine therefore has changed fundamentally. In the brain, a cholinergic (ACh) system triggers the brain activity for waking cognition and REM dreams. Again, the same molecule has two radically different roles.

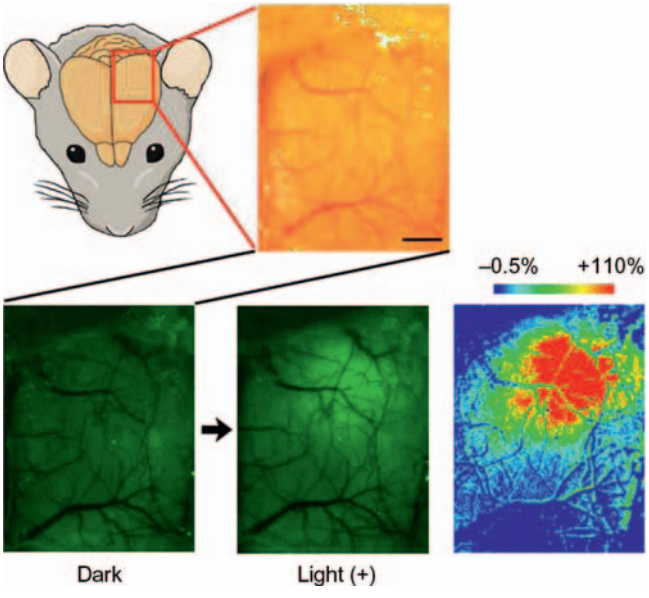

FIGURE 16.4 The mouse cortex: measuring gene expression. Whole-brain gene expression in the mouse. In this figure, a mouse brain is injected with a fluorescent reporter dye that reflects neuronal gene expression by the ARC gene promoter, which is involved in learning and neuroplasticity. Discoveries in other species often cast new light on the genetic control machinery of the human brain. *Source*: Eguchi and Yamaguchi, 2009.

The ACh synapse also revealed an enzyme to deactivate ACh. *Acetylcholinesterase* degrades ACh after it is released. Clean-up is a crucial part of synaptic chemistry, another important point. Without clean-up the synapse would be poisoned by excess ACh. Bioactive molecules are tightly regulated in the body. (The ending *-ase* stands for an enzyme that inactivates a molecule, in this case ACh.)

2.0 GENES IN EVOLUTION, THE LIFESPAN, AND DAILY EVENTS

Genetics was controversial for many years because speculative ideas about racial and ethnic inheritance have been badly abused. It is important to approach it with great care and precision, and with consideration for all of us, because we are all influenced by our genes. Human differences now are viewed mainly as signs of the continent of origin of our more recent ancestors. But these visible differences came about fairly recently. Our hominid ancestors evolved in Africa over millions of years (Figure 16.5). It was only 30 to 70 thousand years ago that *Homo sapiens sapiens* began to spread from Africa to the rest of the world; migrations inside Africa were also very common. The modern human genome can be dated back to a population 'bottleneck' of more than 100,000 years ago, when the proto-human population was believed to have been reduced to about 5000 individuals. Such bottlenecks tend to restrict genetic variation, so that today individual human genomes differ only by 1 or 2%.

Many psychological and brain variables are roughly 50% heritable. The question today is which *specific* genes do what – with regard to disease risk, for example. Humans have *biochemical individuality*, as reflected in our different responses to life-saving medications. We are just beginning to understand many of those issues.

Our *Homo sapiens* ancestors were almost certainly dark-skinned, as an adaptation to the intense sunlight of the equatorial regions. Sunlight destroys *folic acid* in the skin, a crucial B vitamin for reproduction. Excessive sunlight can also cause skin cancer, though a moderate level of sunshine is needed to make the essential vitamin D. In sunnier regions of the world humans evolved higher levels of the skin pigment *melanin* to provide protection from sunlight. It is melanin that tans the skin, and it is differences in melanin that account for different skin colors among human populations.

There is speculation that the first 'behaviorally modern humans' – defined as people who used symbolism,

tools, and fire and had a spoken language – may have resembled the San people of South Africa. However, human brains are strikingly similar across the continents. Our external differences reflect the adaptive histories of human ancestors in different conditions, coping with different temperature extremes, disease vectors, social conditions, and nutrients. Dairy foods require a metabolic adaptation to digest lactose (milk sugar), and many people are lactose intolerant. Some human groups evolved enzymes to metabolize the mother's milk of a different species, like cows or goats.

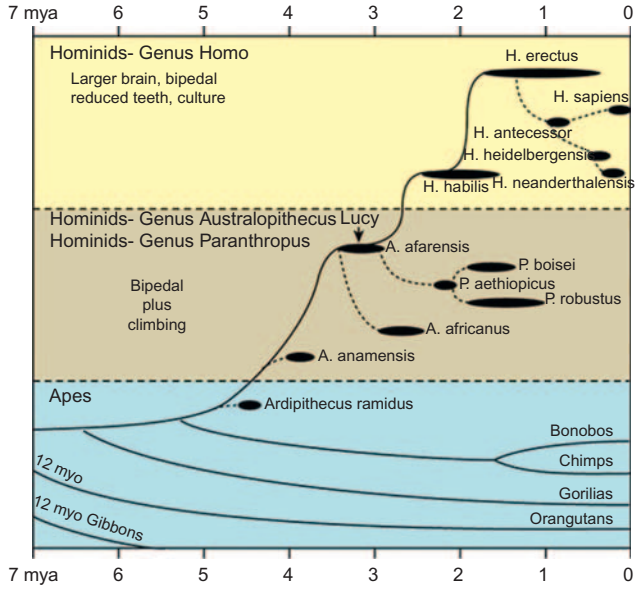

FIGURE 16.5 Four million years of hominid evolution. Human-like creatures have dwelled on earth for about 4 million years, beginning even before the hominid ancestor named 'Lucy' (see above). This diagram shows our current understanding of the emergence of *Homo sapiens sapiens* from ancestral species. Today chimps and bonobos are our closest primate relatives (lower right corner). But a few hundred thousand years ago, different hominids coexisted at the same time (upper-right corner). *Source*: Kaas and Preuss, in Squire *et al*., 2003.

Other recent changes emerged to cope with colder temperatures, toxins, and infectious diseases.

Yet we can see amazing similarities with our ancestors from tens of thousands of years ago. The top of this chapter shows a fragment of the cave art found near the village of Lascaux in southern France around 1940. It is dated about 16 000 years ago. When Pablo Picasso first visited the caves, soon after their discovery, he reportedly said, *'We have learned nothing new'* in making art. Although we do not know how those early people thought, their art gives us a sense of kinship.

2.1 DNA operates over multiple time scales

DNA operates over a remarkable range of time scales. Genes work over geological stretches of time – hundreds of millions of years – as well as generations. For humans, a generation is about 15 to 30 years. But genes operate over the 24-hour cycle as well. They are now known to control the sleep-waking cycle, learning and neural plasticity, the immune response, aging, disease progression, and healing. Your brain is doing some gene-based processing right now to enable you to learn what you are reading at this moment.

Keep in mind that genes play three major roles: they have shaped the evolution of the brain, such as the frontal lobes – including language, social relationships, and the ability to recognize facial expressions. They control the program for lifelong brain development, from fetal growth to aging. And in nerve cells, genes also control moment-to-moment events like learning and falling asleep.

Folklore around the world has long dwelled on family resemblances. There's nothing new in that. But the role of genes in human behavior has been controversial in science. Much of that controversy was resolved a few decades ago when scientists began to do careful studies of twins, siblings, and extended families. Researchers

TABLE 16.1 Twin studies of neurological disease risk

Disease	Monozygotic (MZ) twin concordance	Dizygotic (DZ) twin concordance	λ_s
Multiple sclerosis	25% [54]	5% [54]	20
Autism	75% [60]	16% [60]	45 [61]
Migraine with aura	50% [62]	21% [62]	4 [63]
Late-onset Alzheimer's disease	59% [64]	32% [64]	5
Schizophrenia	50% [65]	4% [65]	10 [66]
Poliomyelitis	36%	6%	
Rickets	91%	23%	
Tuberculosis	32%	14%	

Twin studies helped to establish heritability patterns for genes. For monozygotic (single egg) genes, concordance rates can be quite high and somewhat lower for heterozygotic twins.

found striking correlations depending upon the degree of family relatedness. Identical twins show the highest correlations, followed by nonidentical twins, siblings, and more distant relatives (Table 16.1). In exceptional families certain diseases have been found at much higher rates than the average. They are commonly studied to explore the molecular basis of disease.

A famous example is the KE family in the United Kingdom. This family demonstrated severe speech and language deficits over three generations, called *verbal dyspraxia,* though only about half the family members were impaired. Over three generations the KE family had a high probability of missing a stretch of DNA that came to be called the *FOXP2 gene*, following an inheritance pattern called *autosomal dominant.* A genome scan of family members showed a break in chromosome 7 due to a local mutation.

Speculation became rife that the gene for language had been discovered. That would be important. Previous chapters have discussed Broca's area (the lateral inferior frontal gyrus, usually in the left hemisphere), which is needed for speech production. fMRI scans of the KE family showed underactivation of broca's area while speaking, but also deficits in the basal ganglia and its control of the vocal tract. However, the FOXP2 mutation impaired speech comprehension as well as production.

The fact that humans learn language very early in life, and that our closest living cousins, the chimps and bonobos, do not, suggests there is something different about humans as speakers. Full-blown language and symbol manipulation emerged fairly recently in human evolution, perhaps as late as 50 to 100,000 years ago. FOXP2 therefore aroused a great deal of interest as a candidate gene for language.

Some of that excitement faded when it was found that the same gene is involved in vocal production in songbirds like canaries, as well as bat echolocation, and vocalization in mice, monkeys, and even reptiles. Some birds are talented speakers, like the African gray parrot, but they are not likely to have evolved speech and language for the same functions as *Homo sapiens*. Parrots are excellent vocal mimics and intelligent, environmentally aware, social creatures. FOXP2 may therefore be involved in something humans have *in common* with parrots – and alligators. Its most obvious role might be in the development and control of the vocal tract. It now seems that the FOXP2 gene is involved in regulating *other* genes that guide the growth of the brain, lungs, and gut.

It seems that language is not a single capacity. It is a large set of capacities, some of which we share with other species – like the development of lungs and breathing muscles, moment-to-moment control of breathing and vocalization, the ability to know the world, the ability to act on that knowledge, and to communicate it to others. Scientists are now exploring gene candidates that may play a role in speech and language. That may help to discover molecules to aid people with language deficits, and perhaps even to help the rest of us remember new vocabularies in brain science.

2.2 Brain development: neurogenesis, then synaptogenesis

Genes and molecules play different roles in different stages of development. It is useful to understand this general fact in terms of Gerald Edelman's *first and second repertoire* of neuronal variation and selection. In the *first* repertoire, tens of billions of neurons sprout as the fetus grows, each new cell following its own pathway to make up the brain, spinal cord, and peripheral neurons. Different classes of cells emerge at this time, until, when a baby is born, it will have more nerve cells than it will ever again have in its entire lifetime (Figure 16.6). That is because neurons are constantly being *pruned,* if they make unstable or unproductive connections. The brains of newborns do a lot of pruning, to refine and differentiate their connections. This 'amplification and pruning' are Darwinian in nature, in that the most working neurons and circuits survive, while others die off. Thus functional brain circuits begin to emerge early in gestation, and by the time a baby is nearing birth, most of its hours are spent in a REM-like state, showing an active EEG with rapid eye movements.

Once a fetus begins to use its senses and learn, around the beginning of the third trimester of pregnancy, a *second repertoire* arises. While the flow of new neurons slows down, new *synaptic connections* keep sprouting in the trillions. *Synaptogenesis* now occurs in great profusion, followed by synaptic pruning. In this second stage, Darwinian selection therefore applies to synaptic connections rather than nerve cells. The Hebbian rule applies in that '*neurons that fire together, wire together*' (Chapters 3 and 10). Synapses that make useful connections tend to survive, while unconnected ones may wither. The connectivity pattern of the brain is the key to its working, and this second repertoire of synaptic growth and selective pruning continues throughout life.

In the first repertoire of neurogenesis, when millions of neurons are born and develop, genes and molecules are building the brain and guiding neuronal branches to their targets. Once the basic structure of the brain is settled, the same genes and molecules switch to run

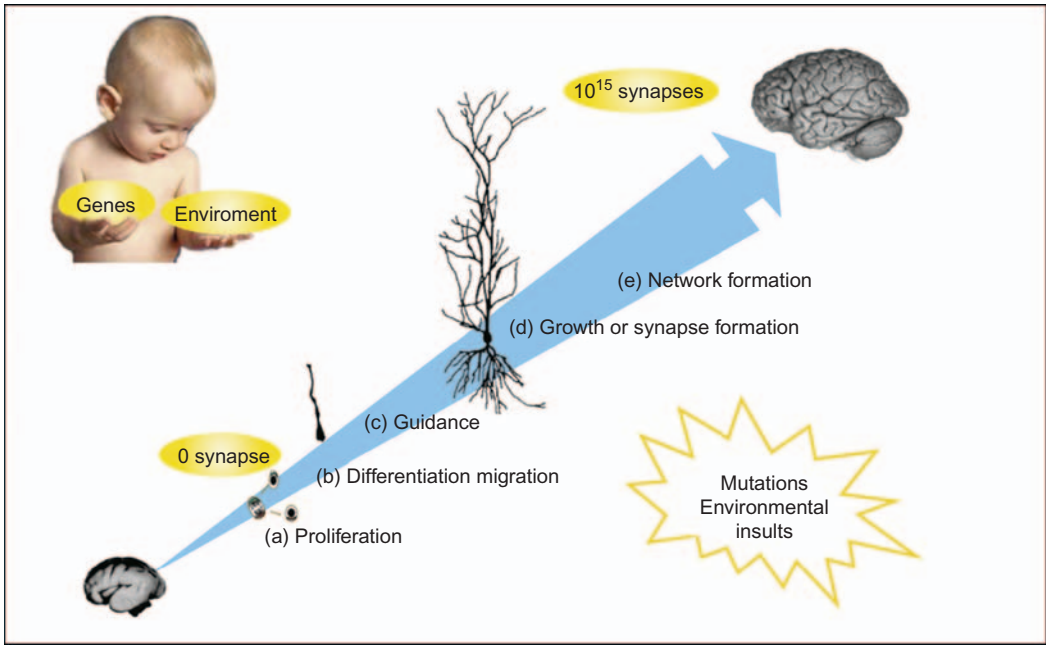

FIGURE 16.6 Environment and genes over the lifetime. Environment and genes interact in all stages. (a) Proliferation: soon after conception neurons multiply and spread, in a process called neurogenesis. (b) Differentiation and migration: cells differentiate in shape and function, migrate, and extend long branches to reach their final form. (c) Axonal guidance is crucial in this still rather mysterious process. (d) Axons and dendrites form synapses with other neurons; successful synapses are kept, and unsuccessful ones are pruned. (e) Working networks enable information processing in the growing brain. Brain development begins with zero synapses and ends with a thousand trillion connections. *Source*: Yehezkel, 2008.

the brain on a day-to-day basis. For example, the normally inhibitory neurotransmitter GABA is actually excitatory in early brain development, when it plays an important role in guiding axonal pathfinding.

The result is a maximum of adaptive variation (Figure 16.7). Keep in mind that humans, like other species, have had to cope with a constant threat of starvation, drought, new diseases, new social challenges, new mutations, new varieties of sexual selection – one of the basic sources of Darwinian adaptation – and many other challenges and opportunities. When humans began to herd goats and cows for their milk, people who lacked the enzymes to digest goat's milk encountered a basic challenge to their health. It all depended upon their biochemical readiness.

Genes and molecules bring disease as well as health. We will discuss cognitive, social, and neurodegenerative brain disorders. But most genes work silently from moment to moment to grow and maintain our brains and bodies.

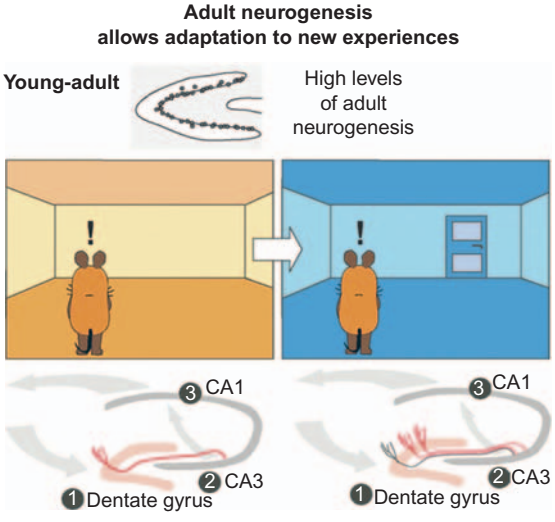

FIGURE 16.7 Neurons are born throughout life. A rat's hippocampal view of landmarks in a maze: if it's orange, do I turn left for food? The hippocampus has place cells in the CA 1 and CA 3 regions, which learn to respond to different landmarks, and even to monitor the speed and bodily orientation of the animal at various choice points in running the maze. Although large-scale neurogenesis stops around the time of birth, a few parts of the brain continue to add neuronal stem cells throughout life. They are the dentate ('tooth-like') gyrus of the hippocampus (above) and the subventricular zone (located below the lateral ventricles). New brain cells may enable greater plasticity. *Source*: Kempermann, 2008.

2.3 How did you get that big brain?

The human brain expanded rapidly over the past few hundred thousand years, much faster than our bodies.

That fact suggests a limited number of genetic changes, but the particular genes responsible are not known. Indeed, there are no other mammalian analogs for the forward fields of the human frontal lobes. However, primates have many brain similarities to other mammals, even ones as small as mice, as shown by the matched colors – the light and dark gray, light and dark purple, red and blue zones of Figure 16.8. The visible core of the brain is conserved among mammals, but the neocortex and frontal lobes have expanded dramatically.

Homo sapiens is marked by a large forward expansion of the cerebral cortex (the prefrontal lobes), which has been called 'the organ of civilization' (Chapter 12). It appears to be distinctive among all living species. The human neocortex is about 1000 times larger than the neocortex of the earliest mammals. Other large-brained mammals, like whales and elephants, also have expanded cortices but proportionally somewhat smaller prefrontal lobes. The most prominent frontal functions are language production, social behavior, and high-level executive control. Language and symbolism are distinctive features of human culture. Executive control allows us to carry out plans and work with others. Social cognition is a key to a cooperative society but also to out-group aggression, and both the serotonin system and monoamine oxidase enzymes (MAO) have been associated with aggression. Aggression may be adaptive for hunter-gatherers, who must be prepared to defend themselves or to kill prey or competitors, but it may become less functional in highly organized social groups.

3.0 GENE EXPRESSION AND REGULATION

All human cells have a complete copy of our species genome in their nuclei, in the form of a long, linear DNA code, twisted into the well-known double helix. The genetic code is *expressed* in proteins that define, develop, regulate, and control the phenotype. In each cell nucleus DNA is *transcribed* into messenger RNAs (mRNAs), which are then *translated* into proteins.

A formal definition states that a *gene* is 'a locatable region of genomic sequence, corresponding to a unit of inheritance, which is associated with regulatory regions, transcribed regions, and/or other functional sequence regions' (Pearson, 2006). There are far more gene-regulatory regions than previously thought. Simple gene-to-protein translation is rare. The genome is an intricate network, not a one-to-one dictionary.

In some cases, like simple Mendelian inheritance in fruit flies, we can see how DNA expresses the proteins

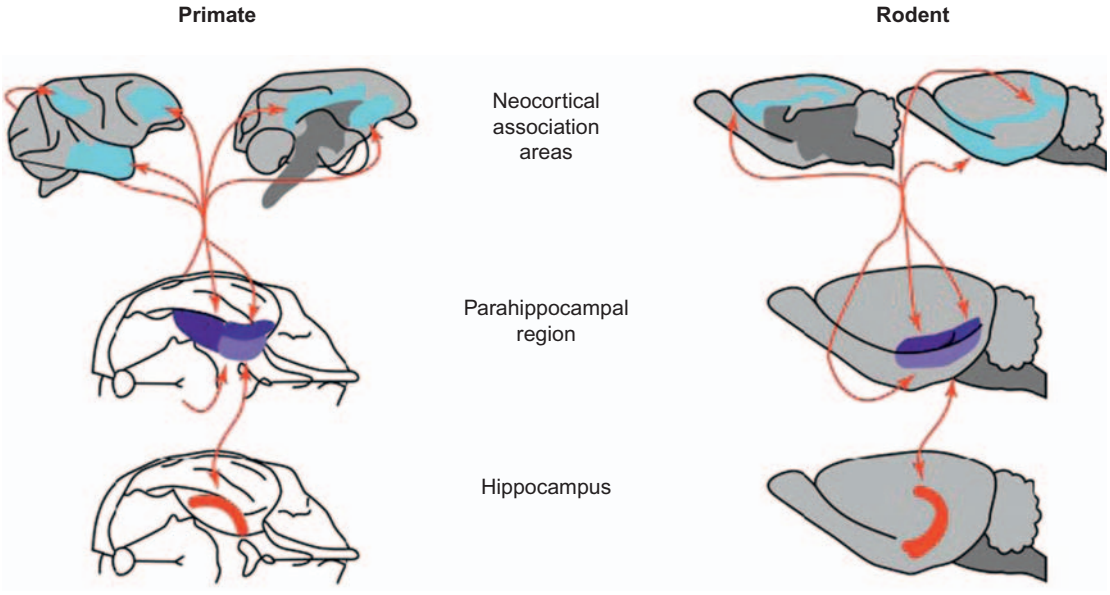

FIGURE 16.8 Of primates and mice. Even though the brains of mice and primates differ, core mammalian areas are remarkably similar (see tinted zones). The hippocampal region is highly conserved among mammals and even birds, and may have close homologies in reptiles and fish. The visible outer brain in humans is mostly cerebral cortex and cerebellum (underneath). In rodents the neocortex looks like a flat layer on top of the olfactory brain. The neocortex is in fact a flat, six-layered structure, but in humans (and whales) it is so large that we see it only as a deeply folded shape. *Source*: Eichenbaum, 2003.

that code for a phenotypic feature like eye color. But most genes work more broadly and more interactively.

Nevertheless, DNA still is expressed, directly or indirectly, in the *proteome*, a huge collection of species-specific active proteins and their basic parts, the *amino acids*, which have an *amine* group, NH_2, and a carboxylate, COOH. Proteins are the basic constituents of life, along with oils, fats, minerals, and some small molecules.

3.1 Information processing in the cell

The Central Dogma has three information-carrying molecules, and three basic steps between them (Figure 16.9).

1 *DNA-to-DNA replication.*
The first information transfer comes with reproduction, where the DNA from the father and mother are passed to their child. This DNA-to-DNA transfer is called replication, and traditionally it has been viewed as a protected code that is almost never altered, with the exception of random mutations. Most mutations are believed to be dysfunctional and tend to die out. That it why it is thought, for example, that species like sharks have remained largely unchanged over hundreds of millions of years. Since all physical systems lose structure and information over time, according to the thermodynamic law of entropy, achieving that kind of constancy over hundreds of millions of years is an extraordinary feat of the genetic molecules.

DNA-DNA replication is not believed to change the code, except in the case of mutations and genetic drift, mechanisms that allow for adaptation when a species encounters environmental pressures affecting its survival and reproduction.

2 *Transcription: DNA to messenger RNA.*
DNA, the blueprint of life, is copied into messenger RNA by a process called transcription. We can still think of this as a copying process. However, molecules called 'transcription factors' have a powerful impact on this stage of DNA expression.

3 *Translation: mRNA to proteins.*
All of life involves proteins, chains of amino acids. Muscle and organ tissue is mostly protein. The control system of every cell, DNA and RNA, enzymes, and transcription factors are proteins (Figure 16.10). They provide the major structural and functional elements

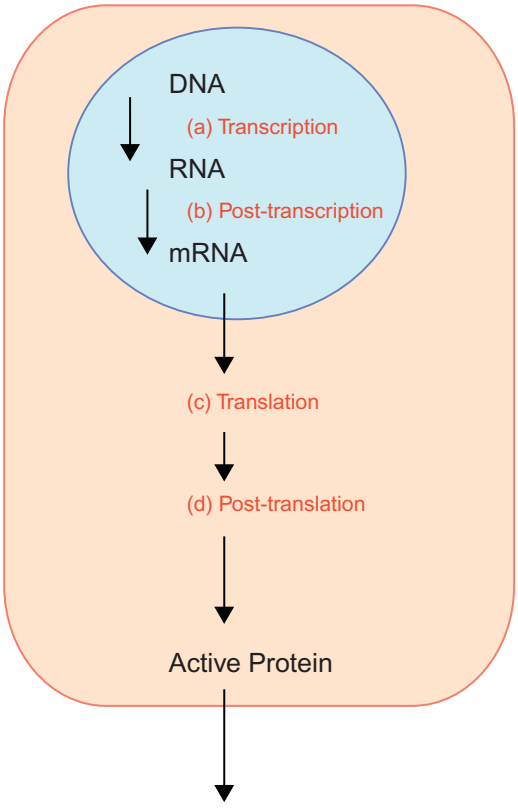

FIGURE 16.9 Gene expression: the Central Dogma. The assembly line of life. The Central Dogma of molecular biology claims that molecular causality flows *from genes to messenger RNA to body proteins*, but not the other way around. It has been challenged by a number of interesting discoveries, but we begin with the Central Dogma and touch on exceptions later. *Source*: Baars.

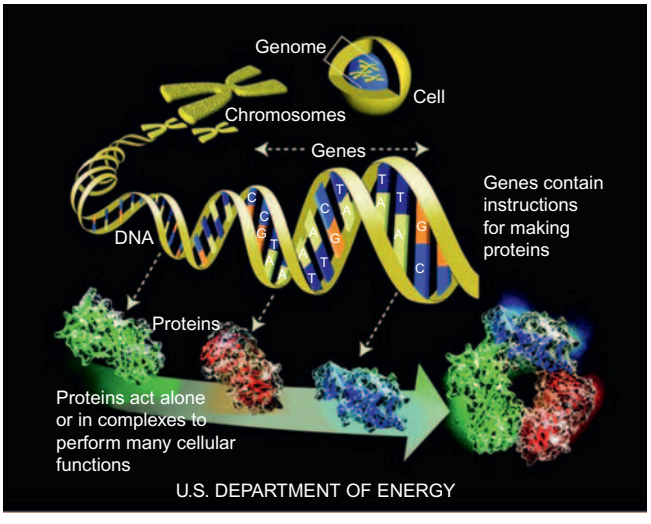

FIGURE 16.10 DNA: simple units combine in endless ways. Considering the complexity of living organisms the basic elements of the genetic code are amazingly simple. Four amino acids make up the base pairs that constitute the letters of the genetic code for all organisms (G = Guanine, T = Thymine, C = Cytosine, and A = Adenosine). The figure illustrates chromosomes in their characteristic x-shaped form at the control center of every living cell. The chromosomes consist of DNA surrounded by molecules that can turn on and off specific sections of the DNA. *Source*: U.S. Dept. of Energy.

of the body. The translation from RNA to proteins is the final step in the chemical factory of the cell.

3.2 Higher-order DNA regulates other DNA

By far most DNA is 'noncoding' and is not directly expressed in active proteins. About 3% of the noncoding DNA seems to perform regulatory functions, controlling other stretches of DNA. Examples include the body-plan genes, genes that control the sequence of brain development, and those that control the circadian cycle. We can think of those as spatial and temporal plans.

Homeobox genes, called Hox, are highly conserved among vertebrates. That is why mice and humans and even salamanders have a long body axis, with two hindlegs and two forelegs, a longitudinal digestive tract, a spinal cord with a brain on top. Body plan genes control other genes that guide the growth of limbs and organs. The point is that Hox is easy to understand as a set of higher-order genes that control and interact with many local genes. Figure 16.11 shows how a set of Hox genes define the anatomy of the upper body, neck, and head in a wide variety of organisms. Figure 16.12 shows how some internal regions of the brain are also regulated by members of the Hox gene family.

Hox genes work via *transcription factors*, proteins that affect the transcription of DNA to RNA. This is one way for the flow of causality to go in a nonclassical direction. Many steps on the classical pathway from DNA to active proteins can be modified by regulatory stretches of DNA.

In order to develop the distinctively human large frontal lobes the DNA body plan must know where to start adding neurons, and at which stage in the developmental sequence. A plumber may need to understand the overall house plan to know where to put a water faucet. The growth of cortex also has to take place in the context of the overall body plan. The body plan is therefore one kind of 'higher-level' regulatory plan for features of the brain.

Failures of regulatory genes can be serious. Some brain diseases are developmental errors, flaws in the moment-to-moment genetic control of neuronal growth. On the other side, regulatory genes also present potentially valuable targets for medical drugs. We will see some examples of both.

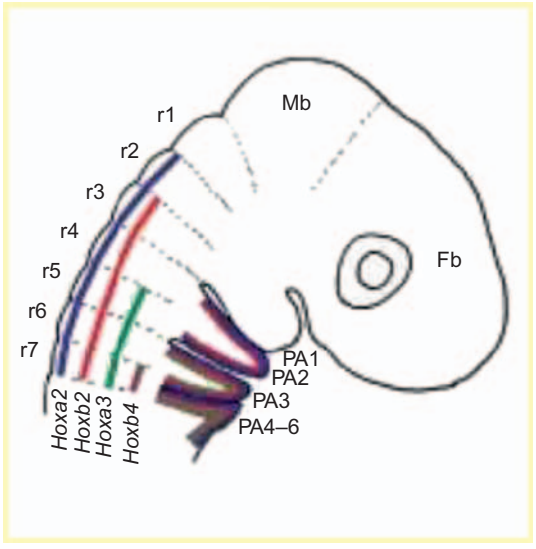

FIGURE 16.11 Hox genes determine tail-to-head positioning. Nature observers have long realized that there are great similarities even between very different organisms. One of those is the bilateral symmetry of humans, mammals, reptiles, and fish. We now know that such basic body plans are controlled by Hox genes, which are 'ultra-conserved,' with an extraordinarily wide distribution in the animal kingdom. There are of course other body plans as well, as in squid and crabs. *Source*: Chambers and McGonnell, 2002.

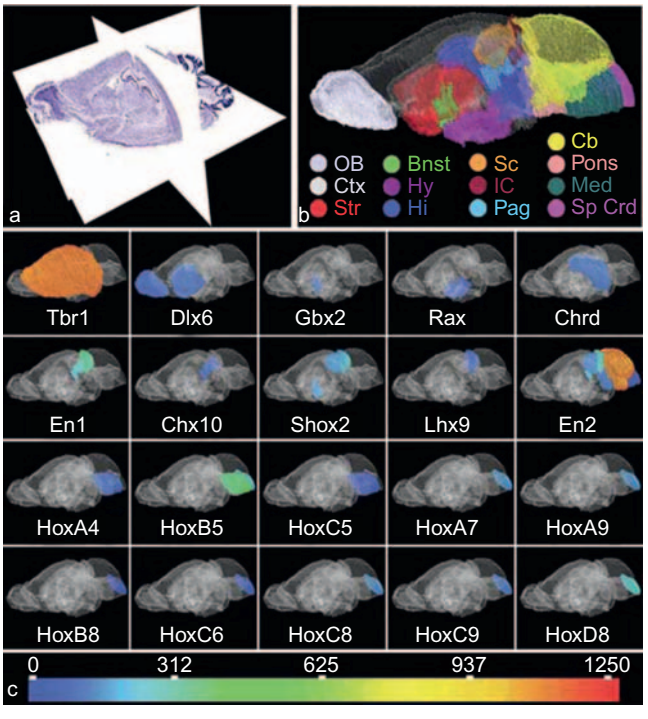

FIGURE 16.12 Hox and brain anatomy. Hox body plan genes also control the development of some brain regions. Notice the three-dimensional brain atlas (a), and the color-coded atlas of mouse brain regions (b). The large panel shows the levels of molecular expression of Hox genes (and some others) in the mouse brain. *Source*: Zapala *et al*., 2005. Reprinted in Zapala, Barlow, and Hovattaã, 2009.

3.3 An error in brain development

To understand the development of the neocortex we can study genes that regulate growth, and also those that may underlie a *failure* to grow. Currently about half a dozen genes appear to regulate the size of neocortex; however, there may well be more. A gene called *microcephalin* was discovered in families at risk for *microcephaly*, in which the growing brain is displaced by cerebrospinal fluid. Somewhat different birth defects are called *anencephaly* and *hydranencephaly.* One lesson from growth failures of the neocortex is the extraordinary adaptability of the infant brain even under adverse circumstances.

The condition called *hydranencephaly* is perhaps the most baffling example. Babies with that condition appear to have no neocortex at all (Figure 16.13). It is now believed that part of the cortex may grow *in utero*, but that for unknown reasons it breaks down and is absorbed before birth. The early cortex may be able to transfer some of its capabilities to neighboring tissues before it is lost. Although most babies with this condition die in the first year, some of them live longer and seem to show surprising behavioral capacities (Figure 16.14).

Hydranencephalic babies may seem normal during the first few months and bond with parents and siblings. When the symptoms finally become obvious, it may be difficult for families to come to terms with their loss. Parents have formed support groups that give more information on the web.

3.4 Development-controlling genes

One way evolution makes a quick fix in the face of a sudden environmental change is by changing a developmental stage. For example, anthropologists believe that the human skeleton is more *gracile* than Neanderthals were; that is, it is not as big-boned, robust, and well-protected. One way to make a robust body more gracile is by expanding its childhood and adolescence. Such 'juvenilization' occurs often. For example, cats and dogs may have become domesticated by way of selective juvenilization, since young mammals become more easily attached to mother substitutes

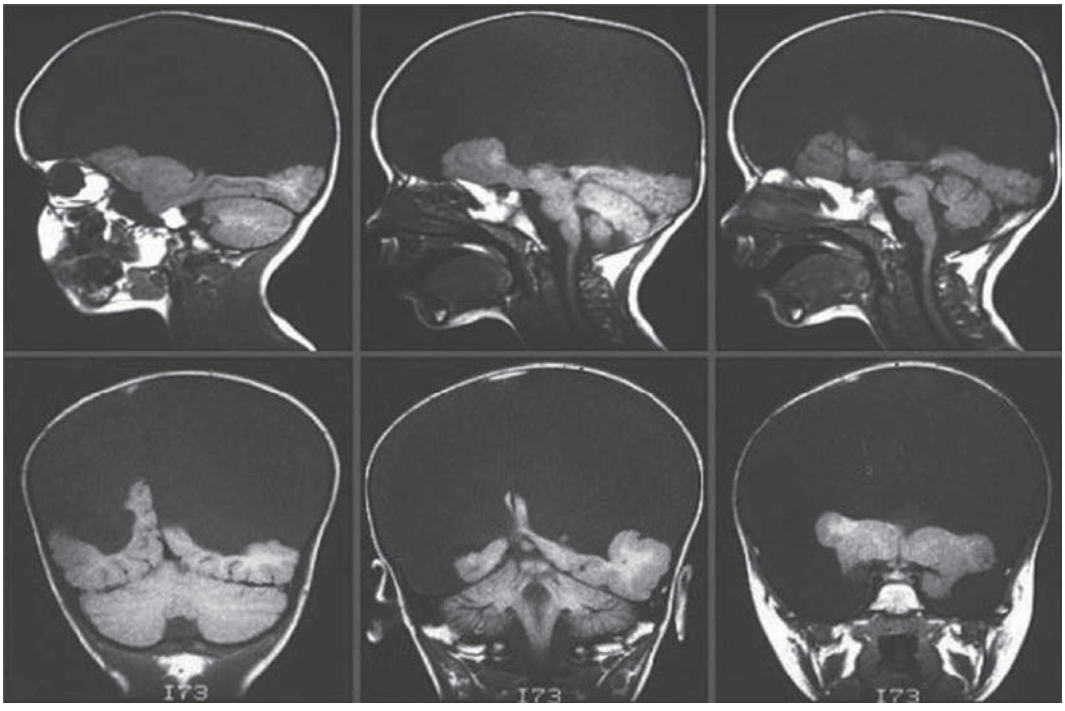

FIGURE 16.13 Missing cortex in a hydranencephalic child. An MRI scan of a baby with hydranencephaly. The dark upper half of the cranium in the X-ray photos is filled only with fluid. The cerebellum and brainstem appear to be intact. The basal brain is responsible for basic sleep and arousal, and the child may seem to seem to have normal sleep-waking cycles for some time after birth. The surprise is that babies with hydranencephaly may behave somewhat normally, and only reveal visible deficits over a period of months. The cause of this disorder is not currently understood. *Source*: Merker, 2007.

FIGURE 16.14 Some children may appear relatively normal without a cortex. Young children born with *hydranencephaly* (the little girl on the right) still show many behaviors that look relatively normal and that encourage bonding with caregivers. *Source*: Merker, 2007.

than adults do. From the viewpoint of our pets humans may be substitute mothers and pack leaders.

Juvenilization is another example of a *regulatory* change in DNA, a higher-level plan that modifies other stretches of DNA. Regulatory genes may be a promising target for drug design, since they exercise such extensive control. Changing developmental stages can allow a whole suite of traits to be altered in a short time. The interaction between evolution and development has become a vigorous research frontier, sometimes called 'evo-devo' for 'evolution and development.'

FOXP2 is such a developmental gene. In a wide range of species it seems to be needed for developing the lungs and vocal muscles. DNA extracted from Neanderthal bones shows the same version of FOXP2 that humans have. However, Neanderthals apparently had less developed symbolic and language capacities. The FOXP2 story remains unsettled.

3.5 Gene programming: beyond the central dogma

If you stay up all night studying for an exam you are mildly affecting the genetic program that keeps your body in synch with the light cycle. If you do that many times, some long-term change can take place. Gene expression in human brain cells can be changed, within limits, by selectively turning stretches of DNA on or off (Figure 16.15 and 16.16). Such 'epigenetic' flow of control runs 'on top of' (epi-) the flow of normal top-down causation.

The discovery of epigenetic programs shows that the network of causation is even more complex than scientists used to think. For example, the environment of the fetus during pregnancy is shaped by the mother's health, alcohol and drug intake, and stress levels. Even the quality of maternal care can change epigenetic regulation. *Fetal alcohol syndrome* is an epigenetic disorder in which a pregnant woman's alcohol intake acts to retard and distort fetal brain development. Not all epigenetic disorders are due to substance abuse, of course. Environmental toxins are also believed to have epigenetic effects over the human lifespan. Some scientists think that *autism* may be an epigenetic disorder, neither completely genetic nor environmental, but a result of some unknown gene-environment interaction.

In sum, molecular biology has become less of a one-way street and more of a network of genes, gene products, and environmental inputs.

3.6 The environment can restructure chromatin in the cell nucleus

Chromosomes consist of long stretches of DNA, wrapped into tight bundles in the cell nucleus and surrounded by a host of support molecules. Humans have 23 chromosome pairs with an estimated 30 000 genes. DNA wraps around histone spheres, proteins that give the chromosome a more compact structure,

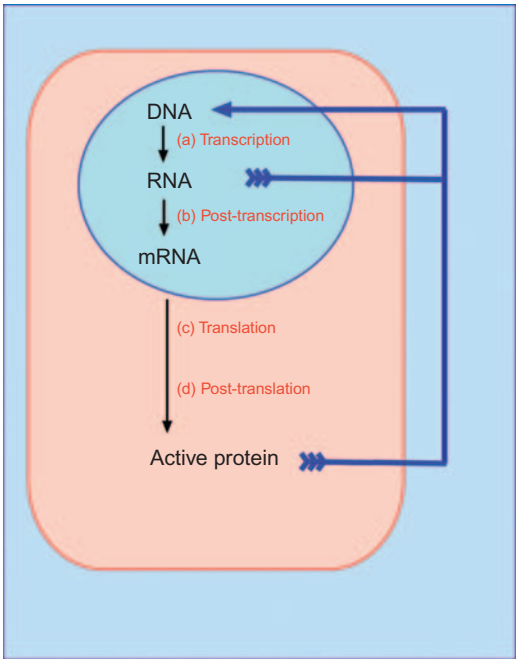

FIGURE 16.15 Epigenetics: environmental shaping of gene expression. In what is sometimes called the 'third genetic revolution' biologists have discovered that the flow of control in the cell does not only go downward from DNA to RNA and then to active proteins. A number of environmental conditions can silence stretches of DNA, or activate them, or change the relationship between DNA, RNA, and the final protein product. *Transcriptional regulation* occurs at the level of the transcription between DNA and RNA. *Source*: Baars.

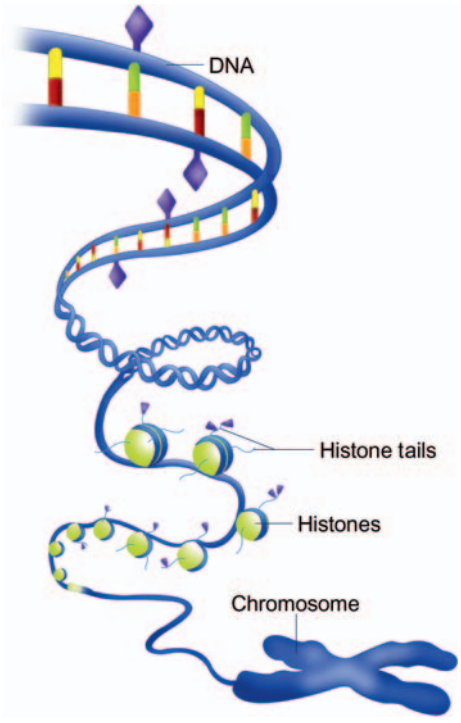

FIGURE 16.16 The epigenetic code can switch gene expression on and off. Epigenetic influences can silence or activate DNA stretches. Histone spheres (light green) act as spools to wind long strands of DNA (blue) into compact bundles, thereby packing almost two meters of DNA into a hundred micrometers of chromosomes in the cell nucleus. To turn stretches of DNA on or off, parts of it must be unwound from their histone spools. *Source*: National Institute of General Medical Sciences, 2009.

like a ball of yarn; together, they form a substance called *chromatin*.

Cocaine and other external agents can alter the configurations of these proteins. Depending on the type of chemical change, chromatin either bunches up or stretches out, activating or silencing genes along the DNA sequence. *Chromatin reshaping* seems to underlie healthy adaptations such as learning and memory as well as disease processes – including cancer, seizures, schizophrenia, and depression. Medicines like antidepressants also seem to reshape chromatin, in addition to other molecular actions.

In rodents, maternal touching and licking has the effect of unwinding neuronal DNA strands from histone spools, thereby allowing RNA polymerase to enable DNA transcription to mRNA followed by protein translation. Lower maternal care will tend to 'silence' DNA by keeping it tightly wrapped on histone spools. The chemical factors involved are TSA (trichostatin A) and the methyl donor methionine. In Figure 16.17, the green tags marked A refer to acetylated histone tails,

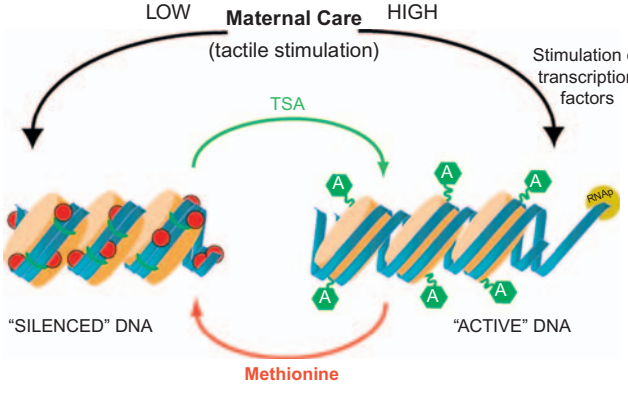

FIGURE 16.17 Maternal care can modify DNA expression. Maternal grooming of rodent pups can facilitate or inhibit DNA expression. *Source*: Champagne and Curley, 2009.

which allow the unwinding and exposure of DNA. At the right end of the diagram the tag labeled RNAp refers to RNA polymerase, the molecule that enables DNA transcription via messenger RNA.

3.7 Learning as an epigenetic process

As we will see, epigenetics now has become crucial to the study of learning. Neurotransmitters alter the gene expression of their cells of origin *and* their target cells as well. Since DNA acts as the control program for the production of molecules, including neurotransmitters, this makes sense for the presynaptic cell. But it is equally true for the postsynaptic cell, and for neighboring glial cells as well. These points are covered in more detail in this chapter's section on learning.

4.0 NEURONS AND GLIA AS SIGNALING CELLS

All living cells share fundamental features: a nucleus with genetic control machinery, cellular organelles like the energy-making mitochondria, basic metabolic digestion of oxygen and glucose, and waste disposal of toxins, all held together by a two-layer lipid membrane. All cells communicate by way of signaling molecules that can pass via the membrane under well-controlled conditions. Neurons are like other animal cells in these respects; but they also are specialized in electrochemical signaling and computation.

To accomplish the job of neurocomputation and signaling, neurons are the most highly branched cell type, serving both as cables and as switching gates, perhaps even as small computers. Neurons are distinctive in being able to send fast electrochemical signals along their long axons, by converting the voltage difference across the polarized membrane into action potentials (see Chapters 1 and 3). Most importantly, neurons synapse onto others, either through the *classical synapse* that was identified decades ago, or by way of a variety of *nonclassical* signaling pathways.

Recently glial cells, the 'glue' that was thought to hold neurons in place, have been found to be bigger players in the brain signaling drama. Glial cells constitute about half of the total mass of the brain. That suggests important functions. Traditionally they have been billed as the supportive players for the biggest actors on stage, the neurons, but glial cells can seize the spotlight as well. Glia do their own kinds of signaling, using calcium waves that propagate more slowly than neurons fire their axonal spikes. But neuroglia also interact with faster neurons via neurotransmitter molecules, and they are the only place in the brain where the Big Two neurotransmitters actually are made (GABA and glutamate).

4.1 Neurons and synapses as on/off switches

A neuron can be considered as a switch, a biological version of the electronic switches in computers. The axon either fires or it does not, flipping between 'send' and 'don't send.' In the same way, the synapse acts as a switch, either allowing chemical transmission or blocking it. The input branches of each nerve, the dendrites, can be viewed as integrators, adding up the voltage inputs from tens of thousands of incoming signals over a very brief period of time. These graded voltages act somewhat like an analogue computer. The flow of information can therefore be stopped, modified, or amplified in each nerve and at each synapse. Although brains are not identical to computers, they are similar in allowing a very large set of switch-like elements to detect, transform, analyze, filter, test, store, retrieve, plan, and control information. Since the brain has about a hundred billion nerves, and trillions of synapses, it can be thought of as a massive collection of information processors, somewhat like the World Wide Web.

It is just as useful to think about the brain as a giant *adaptive* organ. In some ways it resembles a biological species, constantly engaging in massive synaptic reproduction, variation, and selection. But rather than taking millennia, the brain does its Darwinian selection over second, minutes, and hours.

Notice that all processes in Figure 16.18 are self-regulated to ensure that concentrations of biomolecules stay within tight limits. That is the role of autoreceptors for controlling synthesis and release, and therefore the resulting neuronal firing rate. Transporter molecules recycle neurotransmitter molecules back to their sources to be reused. ('Vesicular transporter' refers to molecules being recycled to the vesicles, small bubble-like capsules that ferry neurotransmitter molecules to the synapse.) Metabolizing enzymes may chop neurotransmitter molecules into pieces to inactivate them and recycle their parts. Notice that membrane receptors look like tiny threads, which wind in and out of the membrane. That symbol serves as a reminder that membrane receptors are proteins, long chains of amino acids, which can be classified by the number of times they are threaded into the membrane.

The crucial question is how messenger molecules are made, ferried to the synapse, and released and how they are recognized – or blocked – at the postsynaptic cell membrane. Finally, the target cell needs to convert incoming molecular signals into new membrane voltages, ultimately sending another spike whizzing down its own axon (Figure 16.19).

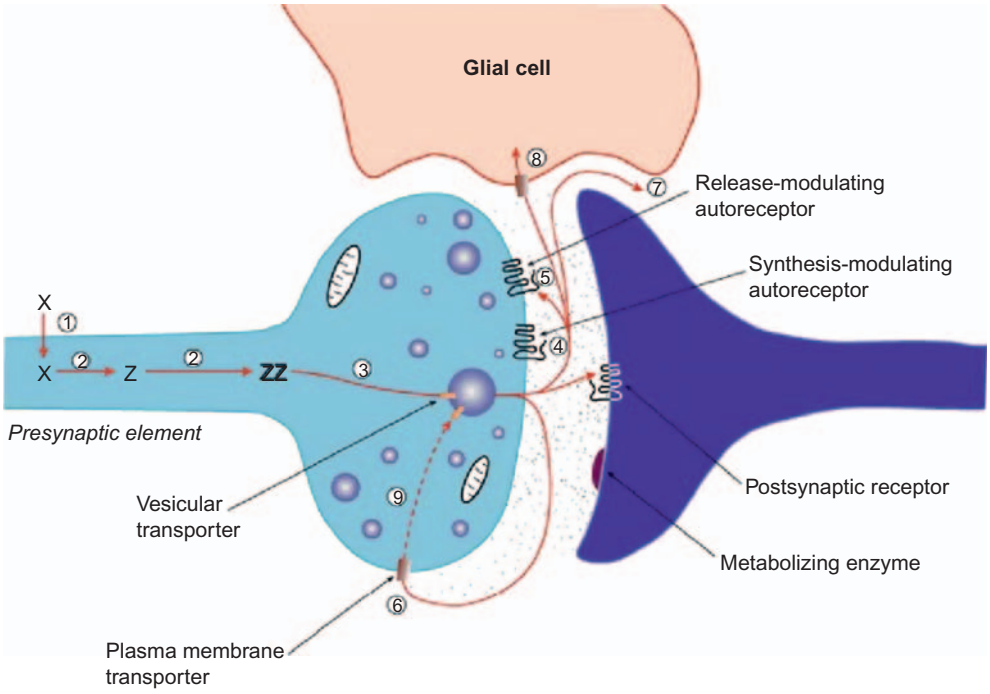

FIGURE 16.18 A basic synapse. Two neurons separated by a synapse, with neurotransmitter molecules released from the first cell and diffusing across the synaptic cleft to the second cell. It is convenient to call the first neuron presynaptic and the second one postsynaptic. The glial cell on top performs support functions, but neuroglia are now known to do their own information processing as well. It is therefore useful to think of synapses as involving three cells: presynaptic, postsynaptic, and glial support. *Source*: Byrne and Roberts, 2004.

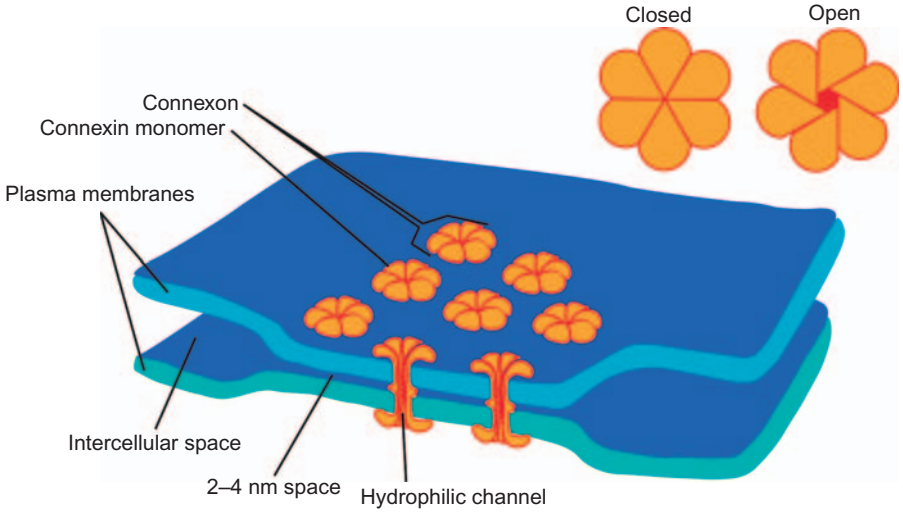

FIGURE 16.19 Gap junctions make direct connections. 'Gap junctions' are direct electrical connections between cells. Most GABA-ergic junctions in cortex are gap junctions, which allow for faster transmission and therefore more precise synchrony among large numbers of cortical neurons. *Source*: Cunningham and LeBeau, in Squire, 2009.

4.2 Chemical self-regulation

Brain chemicals are closely regulated. If the synapse has too little of a neurotransmitter, its message will not be sent. On the other hand, too much of the signaling molecule is generally toxic, and can kill nerve cells. For that reason there are pervasive *negative feedback loops* in any chemical pathway, much like tiny thermostats that keep the quantity of any molecule within safe limits.

In the synapse itself there are many mechanisms to remove excess molecules of neurotransmitters – by turning down the rate of synaptic release, letting molecules diffuse away from the synapse, transporting them back to the originating cell, neutralizing them chemically, recycling them, or allowing glial support cells to vacuum up the excess. Cleaning up the synapse is a vital function. Synapses that become saturated with a neurotransmitter may cease working, and their neurons may die off. A good example is *nitric oxide*, which acts as a neurotransmitter in many synapses – that is how the drug Viagra works – but which turns into a toxic gas if it does not dissipate quickly. Nitric oxide diffuses away from the synapse within milliseconds if the amount is small.

A good example of chemical self-regulation in the brain is the existence of *auto-receptors*. It is vital for neurons to control their own secretions – partly because they can end up poisoning themselves, and partly because too much of a transmitter can fill the synapse with signaling molecules so that it never stops sending the same signal over and over again. If you hear the same message repeated endless times it loses information. The same thing is true of the brain. Neural signaling is only informative if it stops and starts in a meaningful way. For those reasons every neuron must regulate its own secretions of signaling molecules.

4.3 Membranes, ion channels, and axonal spikes

Here is a brief review of our previous discussions of cells and molecules in Chapters 1 and 3.

All animal cells act like tiny electrical batteries, maintaining a voltage difference across their membranes, on the order of −70 to 100 millivolts (mV) (Figure 16.20). That voltage difference is maintained by active membrane pumps, which push positive ions outside of the cell, and negative ones inside. It requires metabolic energy to sustain that difference in electrical charge, and to run other cell functions, so that all nerve cells must constantly consume energy. That is why the brain is such an energy-hungry organ.

Unlike other cells, neurons can convert their membrane voltage into electrochemical signals, as shown in Figure 16.21. The input branches of a neuron accept signals from neighboring cells, which may change the voltage on the dendritic input branches. When these voltage changes add up to about 70 mV near a point at the beginning of the axon, they can 'fire a spike' – a fast

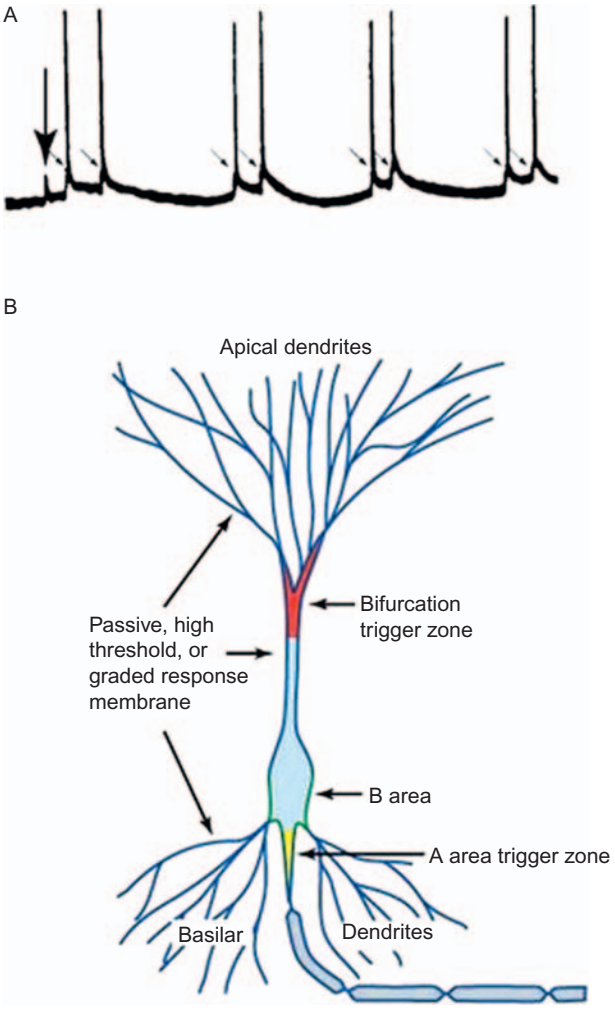

FIGURE 16.20 Basics of neuronal signaling. All cells maintain a voltage difference across their membranes, but only neurons utilize that voltage to propagate an axonal spike. The figure shows how an imbalance between positive ions outside the cell and negative ones inside create a voltage gradient, which must be maintained by constantly pumping ions in the opposite direction. When a spike is fired the charge difference is momentarily lost, and must be reestablished by pumping ions again. The neuron is therefore constantly utilizing energy to pump ions. Source: Shepherd, 2003, in Squire *et al*. Original from Spencer and Kandel, 1961.

wave of depolarization in the axonal membrane. The ions (charged particles) that have been pumped to the different sides of the membrane suddenly are released as the membrane opens up. This sends a wave of electrochemical activity toward the synapses. The axonal membrane voltage drops locally from −70 mV to about +30 mV, but the voltage is restored to baseline within milliseconds. The result is a fast wave of depolarization shooting down the axon from the cell body to the synaptic buttons.

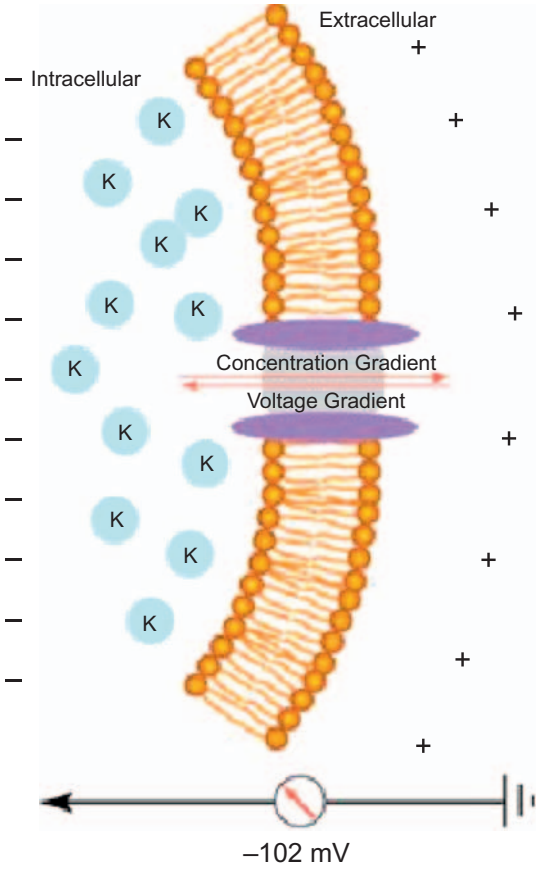

FIGURE 16.21 The cell membrane pumps ions. Lipid bilayers (two layers of molecules) make up cell membranes, pointing toward each other like two matchsticks. The head of each lipid is hydrophilic (water-loving), and the tails are hydrophobic (water-avoidant). As a result, the molecules line up spontaneously in a nanometer-sheet, with the water-loving lipid heads pointing to the surrounding watery medium (inside and outside), while the hydrophobic ends point to each other. Cell membranes are essentially bubbles made of lipid bilayers, protecting internal processes by means of a flexible barrier only two molecules thick. *Source*: McCormick, in Byrne and Roberts, 2009.

This system can be turned on and off, to make a switch, or perhaps a more complex computational element. To excite a neuron we need to depolarize the membrane. That can be done by injecting an electrical current into the cell to reverse its polarity, in much the way you might switch the two electrodes on a battery. Or we can introduce a neurotransmitter into the synapse to signal the postsynaptic neuron to depolarize. The effect is the same. By depolarizing the membrane we send a spike down the long axon, to trigger the release of neurotransmitter into the synapse.

That is the classical model of the excitatory neuron. However, we can also *inhibit* the postsynaptic neuron by *hyper*polarizing its membrane. That is, we can raise the voltage difference across the membrane. The hyperpolarized membrane takes more energy to be depolarized. As a result, we lower the probability that the postsynaptic neuron will fire.

It is easier to see this excitation and inhibition in terms of changes in the spontaneous firing rate of the neuron. Under normal conditions neurons fire at a 'base rate,' even if they do not receive stimulation. A hypothetical base rate might be one spike per second. If the neuron is stimulated by an excitatory neurotransmitter, the rate of firing rises above 1 Hz. But if the neuron receives an inhibitory neurotransmitter the base firing rate may drop to zero. As mentioned earlier, the most common inhibitory neurotransmitter is GABA, while glutamate is the most common excitatory neurotransmitter.

The lipid bilayer forms spontaneously when lipid molecules are put in water. Lipid molecules have one end that is attracted to water (hydrophilic) and another end that is repelled by water (hydrophobic). Lipids therefore couple with their hydrophobic ends toward each other, and hydrophilic ends toward the watery medium. Two-layered membranes therefore form spontaneously, and in the case of cells, become spherical bubbles. The lipid bilayer is both flexible and highly stable, and is highly conserved among living organisms. Proteins embedded in the two-layered membrane form ion channels and pumps, chemical receptors and enzymes, and many other structures to enable hundreds of different processes.

In a sense, all the ion channels we have described in running neurons are voltage-gated. That is, we think of the cell membrane as maintaining a voltage difference between the inside and the outside of the cell. It takes active energy-using processes to make that happen, specifically the ion pumps that are embedded in the cell membrane. We already know that the electrical polarity across the membrane breaks down for some milliseconds, every time a neuron is electrically stimulated, or whenever it generates a change in voltage due to rapid depolarization. Thus electrical events generate a local chemical ion exchange across the membrane, and vice versa, in a very rapidly cycling loop.

Figure 16.22 shows a voltage-gated ion channel at a detailed level. Each type of ion channel can be described chemically in terms of the number of long-chain protein loops that thread to the inside and outside of the membrane. These are called transmembrane segments, with labeled subunits. A fairly simple description like this helps to classify large numbers of membrane-embedded proteins, including ion channels and receptors.

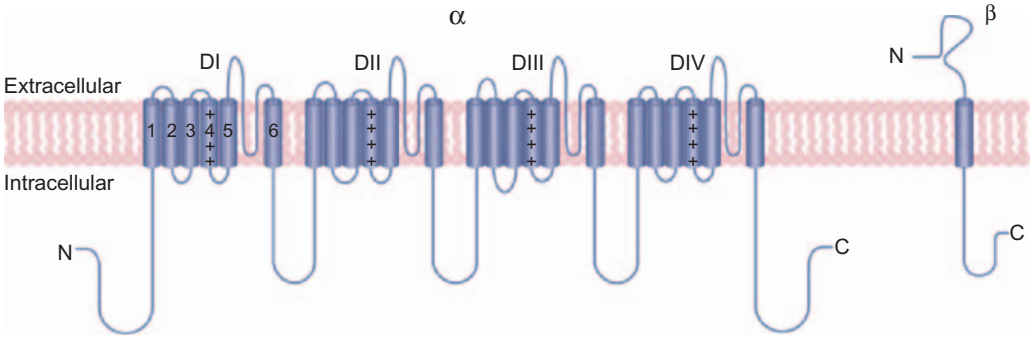

FIGURE 16.22 A voltage-gated ion channel. A voltage-gated sodium ion channel (Na+), with its characteristic long-chain protein looping in and out of the cell membrane with six transmembrane segments, each one repeated four times (DI to DIV). Its two subunits are labeled alpha and beta, and the ends of the long protein thread are labeled N and C (for nitrogen and carbon). *Source*: Squire, 2009 [Encyclopedia of NS].

5.0 SYNAPTIC TRANSMISSION: FROM PRODUCTION TO CLEAN-UP

Messenger molecules in the brain are of two kinds: transmitters and modulators. We can define *neurotransmitters* as having very *local* effects in the synapse between two neurons, although there might be billions of such neurons and synapses secreted by presynaptic cells. *Neuromodulators*, on the other hand, are produced by quite small clumps of cell bodies below the cortex, and are spread very widely. These cells – typically just a few thousand – project their branches through sizable parts of the brain. Where they terminate, they 'spray' their messenger molecules. Thus neuromodulators can change large regions of the brain, while neurotransmitters act locally in nano-level synapses (see Section 6.0).

5.1 The big two: glutamate and GABA

Glutamate and *GABA* are the two most common neurotransmitters in the brain. Ninety percent of the neurons in cortex use glutamate, the primary *excitatory* neurotransmitter, which *increases* the probability of the next neuron firing when a precise number of molecules are released into the synapse. In the human brain glutamate is used in most of the long pyramidal neurons of the cortex and deeper brain structures. It is used at most synapses that are modifiable – capable of increasing or decreasing in strength, thereby making learning possible.

In contrast, GABA is the major *inhibitory* neurotransmitter in cortex. Inhibitory synapses decrease the probability of firing of the next, postsynaptic cell. GABA is used in the bushy interneurons that surround the long pyramidal cells of the cortex, and is considered to be the molecule for 'sculpting' and regulating constant excitatory activity in the cortex.

We do not want *all* our excitatory synapses on all the time. The brain might go into higher and higher positive feedback loops, like a runaway nuclear power reactor. Cortex would be overloaded, as it does in the case of epileptic seizures. An *excess* of glutamate is toxic, called *excitotoxicity*. Much of the damage due to strokes is not direct, but the result of toxicity from an excess release of glutamate. It is just as if an automobile catches on fire and the fuel tank explodes: the secondary explosion can be more destructive than the original fire. Neurotransmitters are useful only in tiny, well-controlled amounts.

Glutamate (abbreviated Glu) is also a good example of the reutilization of preexisting molecules for neural transmission. Glu is one of the dozen essential amino acids that make up animal proteins; these are the ones that cannot be manufactured in the body from other amino acids, and therefore must come from food. The brain therefore borrowed glutamine, one of the basic building blocks of life, to use as its primary excitatory neurotransmitter.

We can also taste glutamate in food, as Japanese researchers discovered in 1907 when they analyzed the residue of soy sauce. The taste of glutamate is one of the five basic flavors for which we have taste receptors, the subtle flavor called *umami*. The taste of glutamate tells us whether food is edible and fresh – essential information for hunter-gatherers trying to survive in the natural world.

We can think of this three-cell system as a tiny factory made especially to produce a tiny, controlled quantity of the neurotransmitter glutamate, transport it to the synapse using small bubbles called vesicles, and squirt each one into the gap to diffuse to the

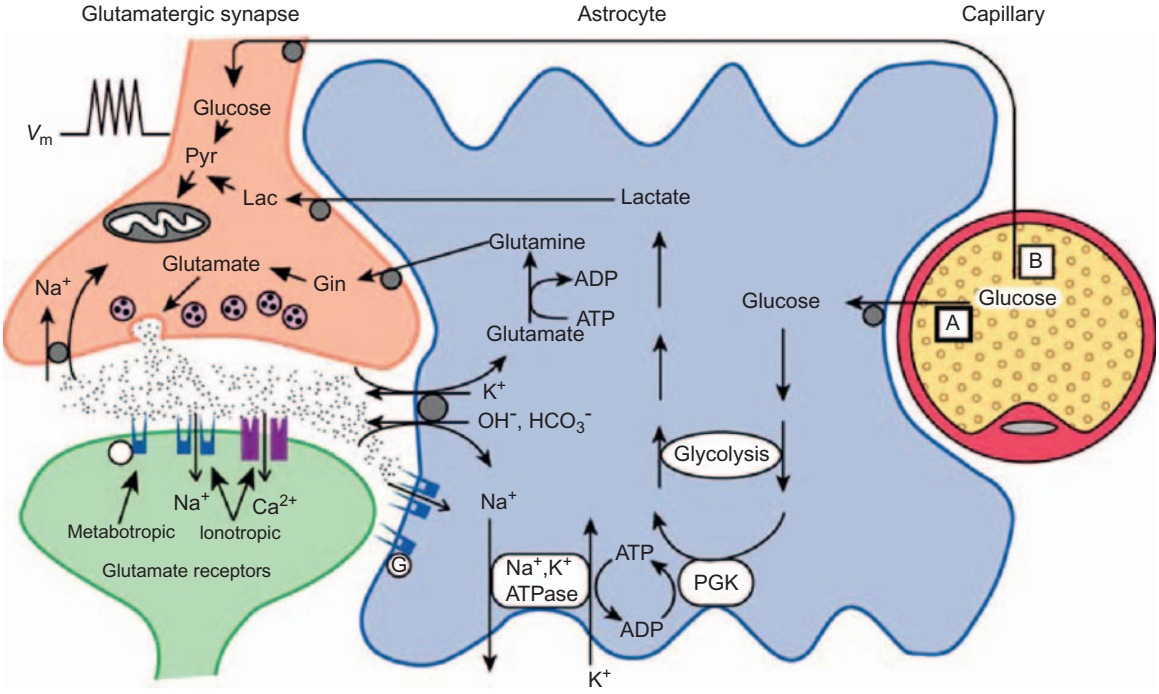

FIGURE 16.23 Glutamate signaling needs three cells. A system of three cells that cooperate to support glutamatergic signaling. On the right side, notice a blood capillary carrying glucose and oxygen to the astrocyte cell and to the two signaling neurons to supply their activities. Glucose also provides raw material for the production of glutamate. (Vm is the membrane voltage of the top neuron, showing all-or-none spikes, which ultimately triggers the release of the neurotransmitter at the synapse.) *Source*: Magistretti in Squire *et al.*, 2008.

postsynaptic cell (Figure 16.23). The tiny oval in the top cell is a *mitochondrion*, an energy-producing organelle. The whole three-cell system is fed directly by glucose and oxygen diffused across the membranes from the blood capillary on the right. As mentioned in the caption, glucose is used for energy and also for the raw material to make glutamate, the neurotransmitter.

Notice that the target cell (postsynaptic) has two kinds of glutamate receptors, which we will discuss later. *Metabotropic* receptors utilize the existing metabolic machinery of the target cell. *Ionotropic* receptors activate the same kinds of ion channels we have seen already: sodium, potassium, and calcium channels.

Finally, the astrocyte (star-shaped) cell in the middle is crucial to the whole nano-factory. It takes in glucose fuel, breaks it down (glycolysis), and converts ATP into ADP for usable energy inside its own mitochondria, squirts glutamine into the presynaptic cell to make glutamate, and soaks up the excess glutamate from the synapse after it is released. The last step is crucial, because glutamate is toxic if it is allowed to dwell too long outside of the cellular machinery. In fact, as we will see, glutamate toxicity is believed to contribute to serious brain disorders. (It is also called excitotoxicity, because glutamate is the most popular excitatory neurotransmitter in the brain.)

If this seems like a lot of trouble to go through just to squeeze out some glutamate in your brain, bear in mind that neurons and glutamate transmission are a very ancient and biologically perfected signaling system. The earliest mammals used the identical molecular machinery 200 million years ago. Even the round worm *C. elegans* has the same machinery. Glutamatergic signaling is exquisitely precise in its timing, and provided the neurotransmitter is cleaned up quickly, it does not leave toxins in the fluid surrounding our brain cells. Almost all biochemical processes produce some toxins (especially oxidation products), and these are very harmful over time.

5.2 GABA: the major inhibitory transmitter

Excitatory neurons are needed to make things happen, but if the brain only had excitation it would go into rapid overload, with every glutaminergic neuron exciting every other one. Inhibitory neurons are believed

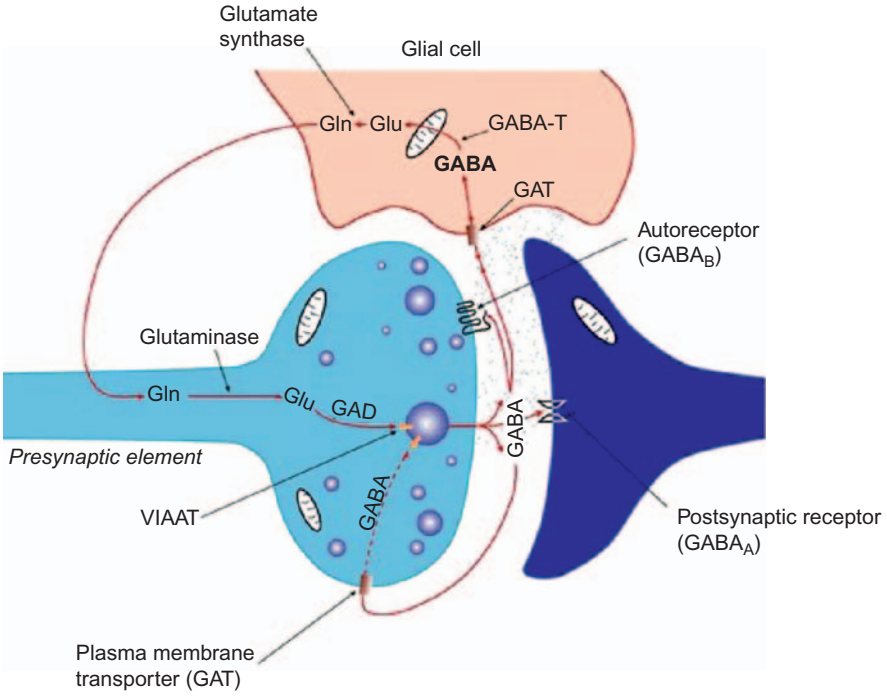

FIGURE 16.24 A GABA synapse. Notice that glutamine-related molecules are used in the production of GABA. A transporter is an enzyme that moves a neurotransmitter molecule back to its originating cell, to be reused. As before, autoreceptors play a role in self-regulation of chemical concentrations in the synapse. *Source*: Deutch and Roth, in Squire *et al*., 2008.

to balance excitatory ones to maintain overall homeostasis in activity levels. Excitatory and inhibitory cells also interact to generate regular rhythms, the most important fast interregional signaling system in the brain.

The glutamate pathway also manufactures the major inhibitory neurotransmitter, GABA (for gamma aminobutyric acid) (Figure 16.24). When a neuron fires and releases GABA, the probability of the next neuron firing is *decreased*. GABA can have the effect of *hyperpolarizing* target neurons rather than depolarizing them, thereby making it less likely for the cell to be fired even if it also receives excitatory inputs. It is therefore the balance of inhibitory and excitatory inputs arriving at a target cell within a very short period of time (~10 milliseconds) that shapes its activity level at any moment (see Chapter 3).

While the long pyramidal neurons of the cortex are excitatory, the smaller bushy interneurons that connect them locally are mostly inhibitory (Figure 16.25). Thus the great ocean of excitatory ripples and waves that keeps the brain constantly stirred up is inhibited locally by dense clumps of GABA-secreting cells. They are called GABA-*ergic*, and the excitatory ones are called *glutamatergic*. (The ending *-ergic* is from a Greek word for exerting force.)

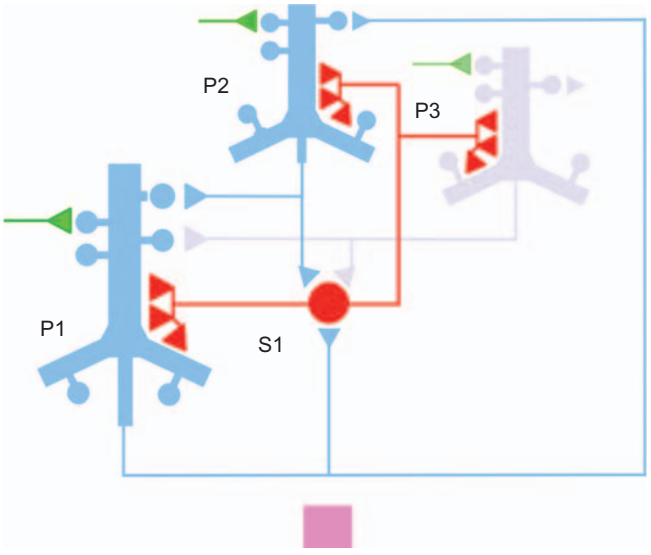

FIGURE 16.25 All cortical circuits involve both excitatory and inhibitory neurons. The pyramidal cells of the cortex are shown in light blue, and the inhibitory interneurons in red. Green neurons coming from outside of the system (perhaps from the visual tract) drive all the cortical pyramidal neurons. S1 refers to 'smooth' neurons, which are also excitatory. Microcircuits like this are pervasive in the cortex, and make for local differences between anatomically similar regions of the brain. *Source*: Douglas and Martin, 2009.

Widespread inhibition is needed to regulate excitatory neurons, and to create boundaries to the flow of excitatory transmission. To prevent excitatory transmission from overloading the brain, there are numerous GABA synapses that regulate the levels of excitation.

GABA is used at the great majority of fast inhibitory synapses in virtually every part of the brain. GABA is also a *behavioral* inhibitor. Most tranquilizers increase GABA-promoting brain activity (called GABA-*ergic*). The relaxing effects of alcohol are also due to its effect on the GABA system in cortex. But GABA has numerous functions, including ones that are more complex than just inhibiting the effects of excitatory synapses.

We can therefore simplify things with some basic principles. Genes operate over many millions of years, over relatively brief human generations, and finally over days, hours, and minutes. The elaborate biochemical dance of molecules makes use of preexisting biological molecules that have been made by living organisms for millions of years. Humans share certain fundamentals with an astonishing range of living and past life forms, but we have important differences as well.

As we will see, those differences are due mainly to higher-level control of DNA, the *regulatory* DNA, rather than the DNA that is directly transcribed into messenger RNA and target proteins. We are not so different from other animals in our basic protein building blocks. Rather, the human difference is in the 'higher-level' organization of our genome, which dictates the growth and operation of the expanded neocortex, especially the frontal lobes. Humans are a new melody played on the basic musical notes of life.

5.3 Neuroglia may also process information

Neurons are the major signaling and information-processing cells of the brain. But they are not the only ones. We have already described the close cooperation between neurons and glial cells. There are many types of neurons and glia, but we will treat them as just two general types of signaling cells.

There is ongoing debate about the exact role of glia in processing information. Neurotransmitters secreted by neurons induce calcium waves that propagate between glia (specifically astrocytes, the star-shaped kind of glia). Astrocytes also respond to visual stimuli with spatially specific receptive fields, like visual neurons. They are selectively sensitive to the orientation and spatial frequency of visual stimuli. Glial cells can act like neurons, therefore. But they are not identical, and there continues to be debate about their respective roles in basic cognitive tasks like sensory perception and memory.

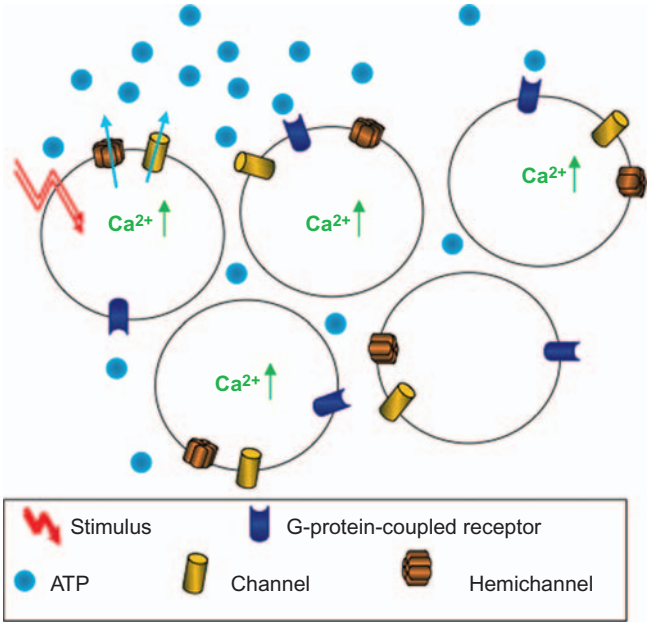

FIGURE 16.26 Glia use calcium waves for signaling. Glial cells can propagate calcium signals to each other by passive diffusion. These cells do not need synapses to communicate. *Source*: Haas and Kettenmann, in Squire, 2009.

Because glia do not need synapses to signal to each other, it is believed that they allow for very fast spreading of activity. This is one type of gap junction. Figure 16.26 shows how a stimulus (the red lightning symbol) can trigger the release of ATP in a single glial cell. ATP evokes calcium waves, which diffuse through adjacent glial cells, generating widespread calcium waves. ATP and glutamate can also increase in the extracellular space, as shown.

5.4 Production, release, and disposal of neurotransmitters

Every cell is a chemical factory. Chemical production starts with raw materials, like the tryptophan in a glass of milk. Tryptophan is converted into serotonin via steps that are controlled by the DNA in the nucleus of the presynaptic neuron. Once the messenger chemical has been made, it is transported to the synapse, often using tiny bubble-like vesicles filled with transmitter molecules. These bubbles fuse with the membrane, and release their molecules into the synaptic cleft.

Production of neurochemicals occurs via a clearly defined assembly line, a pathway or 'cascade' in which each step is enzymatically controlled within very precise limits. Figure 16.27 shows the catecholamine pathway, which results in such fundamentally

important molecules as dopamine, noradrenalin (norepinephrine), and adrenalin (epinephrine). It is possible to influence the amount of molecules by enzymatic action, or by providing precursor chemicals like L-dopa. However, because each step is homeostatically controlled, adding more than the necessary amount of a precursor is not likely to affect the production cascade. By analogy, if an extra ten tons of steel is provided to an automobile assembly line, beyond what is needed to actually make the cars, that steel cannot be utilized. It needs to be stored or disposed of. Because every step in the process is highly controlled, it can only be manipulated from the outside within certain limits. However, if there is a deficiency state, like a folic acid deficiency in pregnant mothers, providing the missing ingredient can be vitally important.

5.5 Synaptic release

Figure 16.28 shows a cartoon of a nerve cell with a classical synapse, releasing messenger molecules into the synaptic gap. The molecules are free to diffuse from the *presynaptic* neuron and are detected by *postsynaptic* cell receptors. There are trillions of such synapses in the brain. Notice that the size of the voltage spikes is affected by recent activity. As the neurotransmitter is secreted into the synapse and therefore decreases in the cell, a fast-following spike can only release the remaining molecules. Again, there is a kind of bucket brigade in the flow of molecular production and release, where the timing of each bucket being passed depends on the timely hand-over of the previous bucket.

In the classic model of the synapse small vesicles (yellow bubbles) transport neurotransmitter molecules down the axon to the synaptic surface, fuse with the membrane, and release their neurotransmitter into the synaptic gap. Other neurons release their neurotransmitters in slightly different ways. Each vesicle may have on the order of several thousand molecules, again allowing for very precise control of its concentration both inside of the presynaptic cell, and in the synapse when it arrives there.

The vesicles carry calcium-binding proteins, which are released as the vesicle touches the presynaptic membrane. It is these calcium-binding proteins that act as sensors to control the moment of neurotransmitter release from their vesicles into the target synapse. Calcium is therefore a major player in the delicately timed and precisely metered squirting of neurochemicals into the synapse (Figure 16.29).

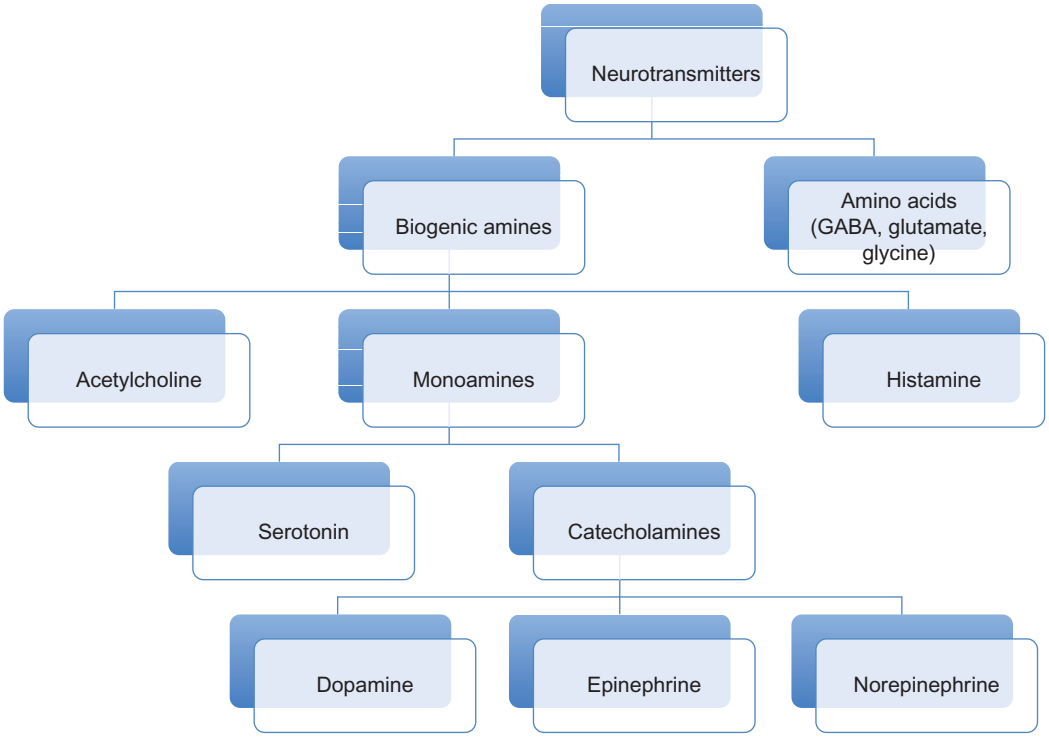

FIGURE 16.27 Catecholamines: a production pathway for multiple neurotransmitters. The catecholamine pathway includes major neurochemicals like dopamine, noradrenalin (norepinephrine), and adrenalin (epinephrine). Thus a single chemical pathway may produce multiple brain signaling molecules. One of these, L-dopa, was made synthetically as the first medication for Parkinson's disease, to increase the quantity of dopamine in the brain. Notice the similar structures of these molecules. *Source*: Baars, 2009.

5.6 Synapses and receptors are traffic control points

Psychoactive drugs typically focus on one specific step in synaptic signaling. Thus L-dopa is prescribed for Parkinson's patients to increase a precursor for dopamine – an ingredient needed in the manufacture of the neuromodulator dopamine. Since Parkinson's disease involves the die-off of dopaminergic neurons in the substantia nigra, L-dopa will stave off its worst effects for some time. (Ultimately, the cells will have to be replaced, however, and much current research is focused on trying to implant dopaminergic cells in the substantia nigra (SN).)

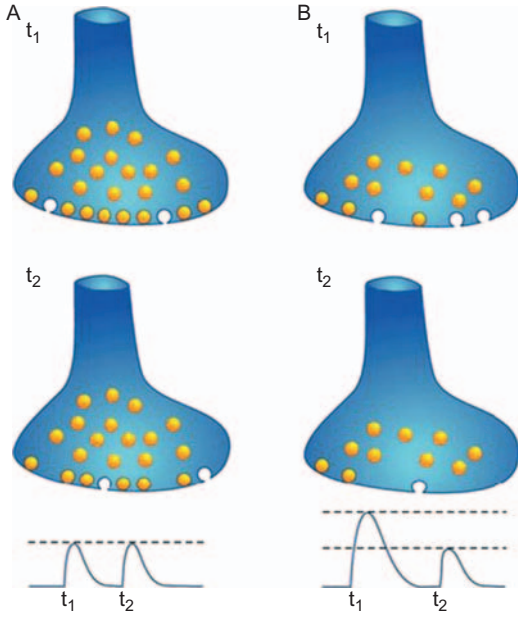

FIGURE 16.28 Vesicles squeeze their molecules into the synapse. A simplified image of the release of neurotransmitter molecules from vesicles (yellow bubbles) that transport the molecules from their site of manufacture, which may be in or near the nucleus, or in other organelles inside of the presynaptic neuron. Vesicles flow in a regulated sequence, often guided by microtubules, essentially submicroscopic tubes inside of the axon. On the left (A), the flow of vesicles leads to release of transmitter molecules in two equal bursts. In (B), the first burst depletes the terminal button, so that the second release is decreased. *Source*: Schwarz, in Squire *et al.*, 2003.

In other cases, the effort is to keep a neurotransmitter dwelling longer in the synapse, so that it can repeatedly stimulate the postsynaptic membrane. A famous example is the selective serotonin reuptake inhibitors (SSRIs) – psychoactive drugs that are effective against depression and other disorders. Reuptake is the rather awkward term for recycling serotonin to the cell of origin, and if you can inhibit recycling you can keep the neurotransmitter around longer.

GABA-ergic drugs like the benzodiazepines increase the amount of GABA in inhibitory synapses in the brain. And we should not forget the role of healthy diets, which supply all of the basic chemistry of the brain, mostly in the form of precursor chemicals, the raw materials from which the cells make all the specific proteins and other products they need.

A great deal of medical research is constantly trying to identify more traffic control points in the body and brain. Channel blockers work by inhibiting the flow of ions like calcium, sodium, and potassium across the cell membrane (important in cardiology as well as brain disorders). These are useful points to keep in mind. While the details are awesomely complex, the basic ideas are actually quite simple.

There are many kinds of neurons and neuron-like signaling cells. Neuroglia were traditionally thought to be only support cells for neurons, but have since been found to do their own transmission and computation. They outnumber neurons by a factor of ten. (The word *glia* originated from the Greek word for the *glue* between neurons.)

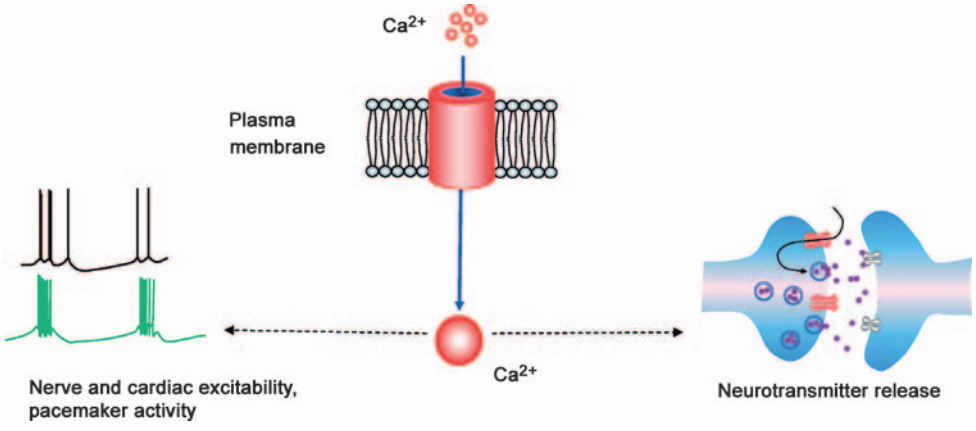

FIGURE 16.29 Calcium triggers neurotransmitter release. Calcium has numerous signaling functions throughout the body. In the brain (and in neurally paced organs like the heart), calcium may be controlled by voltage rhythms. In neurons, a calcium influx may trigger the release of the presynaptic neurotransmitter into the synapse. *Source*: Snutch, in Squire, 2009.

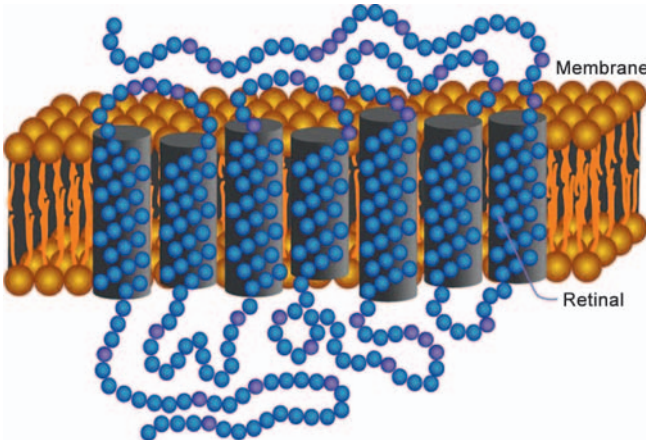

FIGURE 16.30 Receptors are long protein molecules embedded in the cell membrane. Long proteins thread their way across the cell membrane a countable number of times, and form typical membrane receptors and ion channels. *Source*: Squire *et al.*, 2008.

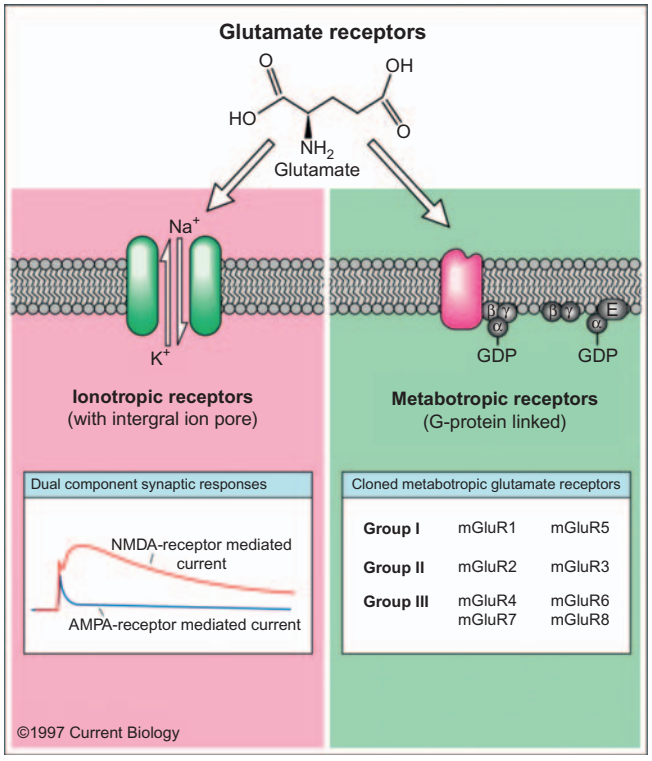

FIGURE 16.31 Glutamate receptors: ionotropic and metabotropic. Glutamate actives two types of receptors, ionotropic and metabotropic. The ionotropic receptors open and close ion channels, just like the sodium and potassium channels that control the local voltage across the neuronal membrane everywhere else. On the right, metabotropic receptors trigger the existing metabolic machinery of the cell, which precedes that evolution of specialized nervous systems. G-protein-coupled receptors are also called 'second messengers.' *Source*: Forsythe and Barnes-Davies, 1997.

5.7 Receptors detect signaling molecules

Receptors can be considered to be the locks into which the floating keys of neurotransmitters try to fit (Figure 16.30). The lock-and-key metaphor is of course the favorite one for describing enzymes and their substrates. In fact, neuronal receptors are special cases of molecular receptors that are a universal feature of the chemistry of life, even in single-celled organisms that have no distinct nervous system at all. The target cell of a neurotransmitter is labeled the postsynaptic cell, while its cell of origin is called presynaptic. Those are obviously relative terms. In effect, we are looking at the synapse as a 'box,' with its input labeled as presynaptic and its output as postsynaptic. If instead we consider the neuron to be the object of interest, what we consider to be the input and output would change. It is useful to keep this shifting focus in mind, to avoid confusion when reading about the microstructure of the brain.

The glutamate receptor has been one of the basic test-beds for neurotransmission. Figure 16.31 shows the prototypical glutamate understanding of glutamatergic (excitatory) neurotransmission. Notice that Glu has two different kinds of receptors, one that is ionotropic (ion-targeted) and a second kind, which is metabotropic, meaning that Glu locks into the existing metabolic machinery of the target cell.

In the first case, we can think of the ionotropic receptor as just a set of ion channels that exchange sodium and potassium from one side of the membrane to the other, such as we see everywhere along the membrane of the nerve cell. But in this case the ion channels are located in the postsynaptic membrane. Ion channels are selective pores, molecular gates that can open and close, either because of a change in voltage or by way of a chemical receptor.

We can take the analysis one level lower and notice that the ionotropic effect of glutamate can evoke two molecular machines, one involving NMDA and the other AMPA. Both of those substances are vital in the process of learning, and we will see their names again. The balance of NMDA and AMPA determines what kind of learning will take place at the target membrane of the glutamate synapse. NMDA is associated with long-term potentiation (LTP), making the synapse more excitable over time. AMPA is associated with long-term depression (LTD), which makes it less excitable. These terms therefore correspond roughly to excitation and inhibition, but not on a momentary

basis, rather in changing the enduring nature of the synapse. From a Hebbian point of view, these are the two logical changes we can expect in the strength of a synapse after learning.

Metabotropic receptors can become very complicated, because they have evolved to take advantage of the preexisting metabolic ballet of the cell. But the basic idea is again fairly simple: it is that the neurotransmitter glutamate locks into a receptor complex that triggers G proteins (G stands for the DNA base pair guanine). G proteins have been studied extensively as part of the basic biology of animal cells, both by way of the universal role of metabolism and of the genetic control machinery of DNA. G-protein-coupled receptors are also called 'second messengers,' because the first messenger (the neurotransmitter molecule) hands on the baton to the second one, and so on. Second messengers can evoke third messengers that even are more deeply embedded in the nuclear apparatus of the cell, and so on.

G-protein-coupled receptors are important for very practical reasons. A surprisingly large number of medical drugs are believed to utilize this level of neurotransmission and metabolic activity.

On the metabotropic side, we have not just two but at least *eight* receptor molecules. We will not cover them in detail. However, it is useful to remember why so many different receptors exist. One reasonable story is that glutamate is involved with 90% of the cortical (excitatory) synapses. But those synapses have many different functions, ranging from visual perception to executive functions and the processing of emotional conflicts. The situation is comparable to computers on the World Wide Web. In one sense, every computer on the Web makes use of the same transmission code (like the ASCII set of letters and numbers). But computers also need to be uniquely identifiable, so that an e-mail message can be sent to the right recipient, who cannot be confused with somebody else. Different receptor types may therefore have the function of uniquely identifying a particular synapse, or type of synapse, perhaps in a particular region of the brain, or subserving a distinctive cognitive function. If the brain makes use of very widespread neurochemicals, it must also have ways of distinguishing among the synapses that use that particular signaling molecule. (In the nature of biology, over hundreds of millions of years of evolution the brain have exploited *both* of those methods of differentiating synapses and their functions. But glutamate and GABA are good examples of very widespread neurotransmitters that inevitably require multiple receptor systems.)

When enough postsynaptic receptors are triggered they can depolarize the postsynaptic cell, either ionotropically by allowing the free flow of ions across its membrane or by triggering deeper molecular mechanisms. Given enough depolarizing molecules coverging in a brief period of time, usually from multiple neurons all impinging on the postsynaptic cell, the new cell can set off a spike in its own axon. Or it may merely experience a voltage change in its input branches, the dendrites. Recent evidence and theory suggest that the graded potentials of the dendrite network may have their own information-processing functions. However, we will focus mainly on the axonal action potential as the primary signaling function of the neuron.

The glutamate receptor has a long evolutionary history, as you might guess from its close relationship with basic biological molecules like glucose and the essential amino acid glutamine. Japanese, Chinese, and French cuisine specialists have long identified the taste component variously called 'freshness,' 'tasty,' 'meaty,' or 'brothy,' which is part of the good subjective taste of protein foods. That taste is now called *umami*, and has been found to be one of the five biologically innate taste receptors located on the human tongue. Biologically, it seems likely that umami corresponds to freshness in flesh foods, like meat or fish. Since mammals must be able to distinguish between fresh and spoiled foods, an umami receptor may confer a significant survival advantage. Chemically, umami involves (among others) the mGlu receptor number 4 (mGlu4), shown in Figure 16.31. Figure 16.32 shows how it looks in detail as a membrane receptor located on the tongue. This is another example of the great generality of biologically fundamental molecules, the fact that they are used over and over again for good reasons in many different species, and for many different functions.

Glutamate is a key to a number of brain-related disorders, including depression, anxiety (especially in its relationship to GABA), and the damage that occurs after a stroke (excitotoxicity). Glutamate synapses are believed to utilize as much as 90% of the energy supply of the brain. They are crucial for learning, and as the primary excitatory neurotransmitter of the cortex, for other cortical functions as well.

5.8 Ion channels that are opened by other molecules

A ligand is a molecule that ties into a receptor (from Latin, *ligare,* 'to tie,' and words like ligament or

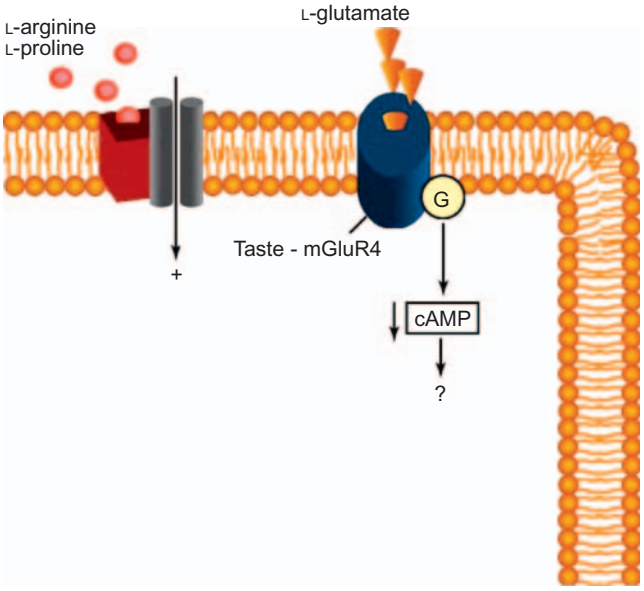

FIGURE 16.32 Umami: the taste of glutamate. Umami is the taste of freshness, according to Japanese, Chinese, and French cuisine experts. It was first isolated from soy sauce in Japan in 1907, and is also an important taste ingredient in many fish and meat broths and sauces. Chemically, umami includes the mGluR4 receptor for glutamate (one of the metabotropic glutamate receptors that is used throughout the brain as well as on the tongue). Other Glu receptors are also involved. Notice that the receptor triggers a G protein that links to cAMP (cyclic AMP), one of the basic energy molecules of the cell. *Source*: Squire *et al*., 2008.

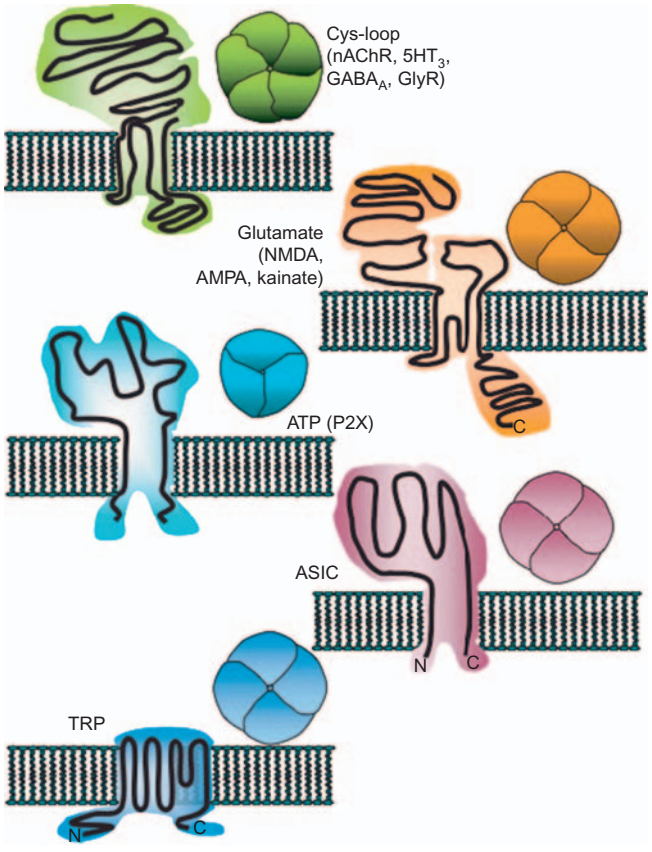

FIGURE 16.33 Ligand-gated ion channels. *Source*: Gopalakrishnan and Briggs, 2007.

ligature in medicine). Glutamine is one of the neurotransmitters that opens ion channels in the target membrane, thereby allowing ions to flow freely, pushing the membrane voltage toward depolarizing. As you can see from Figure 16.33, there are a number of other molecules that can open up ion channels, including acetylcholine, GABA, serotonin (5HT), and glycogen. Each image in Figure 16.33 shows a different ligand-gated ion channel, seen from an imaginary slice through the membrane, and from the outside of the cell. Thus the green image represents a specific 'Cys-loop' receptor for the acetylcholine, serotonin, GABA, and glycogen. (R represents Receptor.) As you can see, the second, orange image shows the side view of the ionotropic glutamate receptor, including NMDA and AMPA, but also kainate (which was discovered more recently). ATP, the energy-carrying molecule, also acts as a ligand to open ion channels.

G-coupled pathways are extraordinarily important. About half of medical drugs are designed to target these pathways. G-protein receptors are sensitive to light, odors, hormones, and neurotransmitters (Figure 16.34).

Given trillions of events per second in the brain, it may seem odd that the cortex has only two major neurotransmitters, glutamate and GABA. In fact more than 100 neurotransmitters are known, and no doubt some remain to be discovered. But the coding possibilities of neuronal information processing is further enriched with a multiplicity of different *receptors* for each molecular messenger (see Figure 16.35 for an example of a neuroimaging study looking at dopamine receptors in human and monkey brains). Thus the same neurotransmitter can have quite different effects in different synapses, depending upon which receptor it activates.

Reutilization is one of the great themes in biology. All land-dwelling animals have lungs to enable O_2–CO_2 exchange. Reptiles like crocodiles can use their lungs as air bellows, to emit roars. Mammals make a range of sounds by forcing air from the lungs to set the vocal cords in vibratory motion, and humans have evolved ways to shape the flow of vibrating air to make vowels and consonants. Vocal speech and language are therefore entirely dependent on the prior adaptation of lungs, for biological reasons that have little to do with speech and language. Reutilization of a prior adaptation occurs at every step in that story.

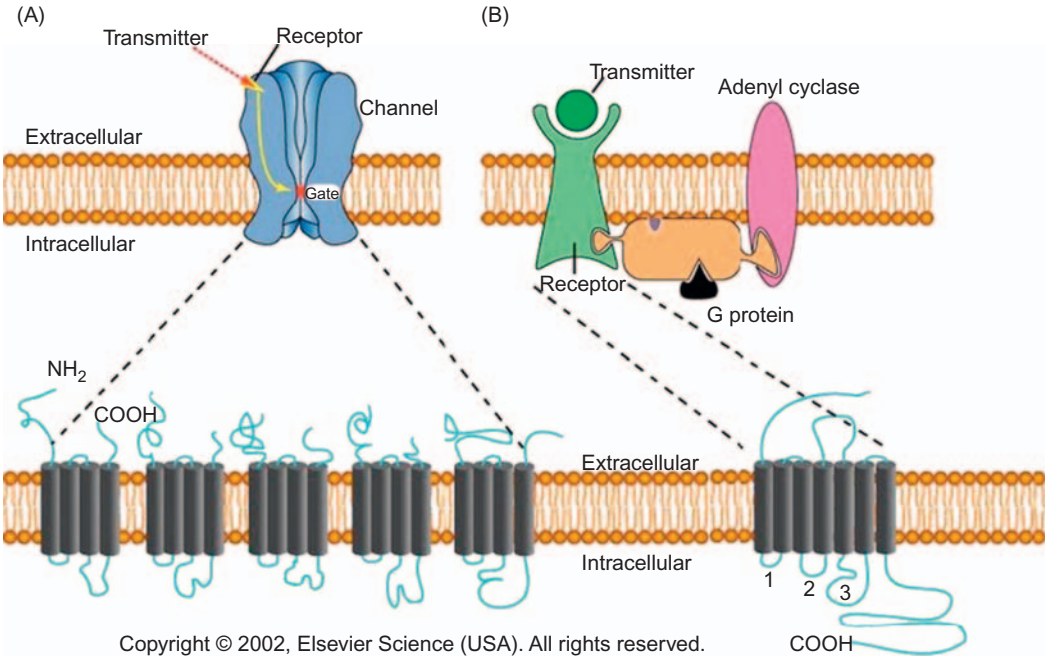

FIGURE 16.34 Metabolic steps triggered by receptors. Above, transmitter molecules dock on a receptor on the left (A), and on a metabotropic G-protein coupled receptor on the right (B). G-proteins are preexisting molecules belonging to the energy cycle of every cell, the cyclic-AMP cycle. As so often happens, the brain reutilizes that basic biochemical process of all living things for the purpose of neurotransmission. The lower level of this figure presents an expanded version of the upper level. Notice that proteins are long string-like chains of molecules, threaded in and out of the double layered lipid membrane. On the lower left, the NH_2 and COOH fractions exist in all amino acids, the constituents of all proteins. *Source*: Squire *et al.*, 2003.

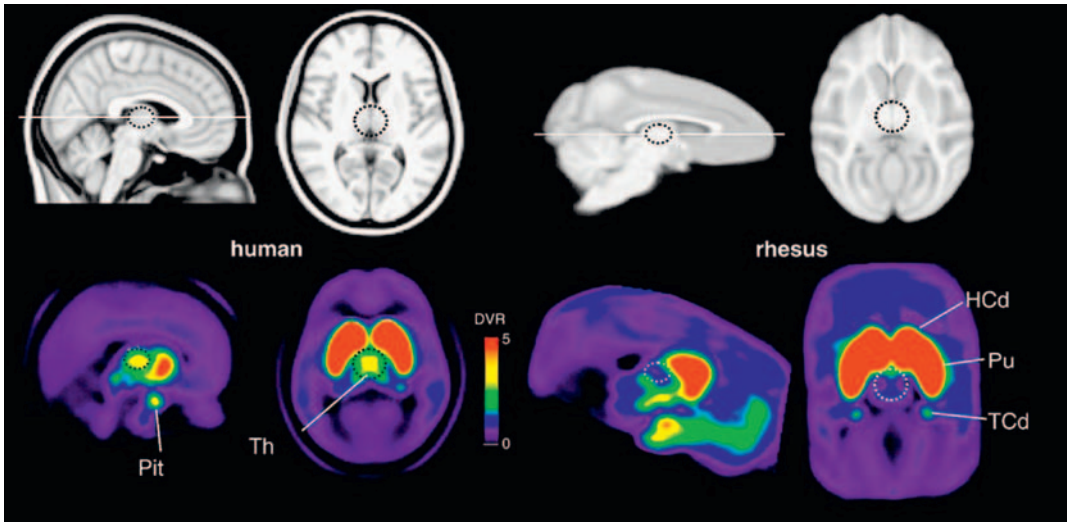

FIGURE 16.35 Distribution of dopamine D2/D3 receptors in the brain. By designing radioactive molecules with chemical affinities to dopamine receptors (in this case D2 and D3), it is possible to record PET scans of the entire brain. On the left, the D2/D3 receptor distribution of the human brain, with the rhesus macaque in the right. Notice the very high levels in the thalamus (Th) in both humans and other primates. *Source*: Christian *et al.*, 2009, Figure 6.

The neurochemicals we discuss in this chapter are pretty much all reutilized for brain functions from an earlier and wider biological role. Glutamate is derived from the essential amino acid glutamine, which in turn is made from glucose, a basic fuel of the cell. Metabotropic receptors reutilize the prior metabolic machinery of each cell. This is an important generalization, because it also allows us to understand and

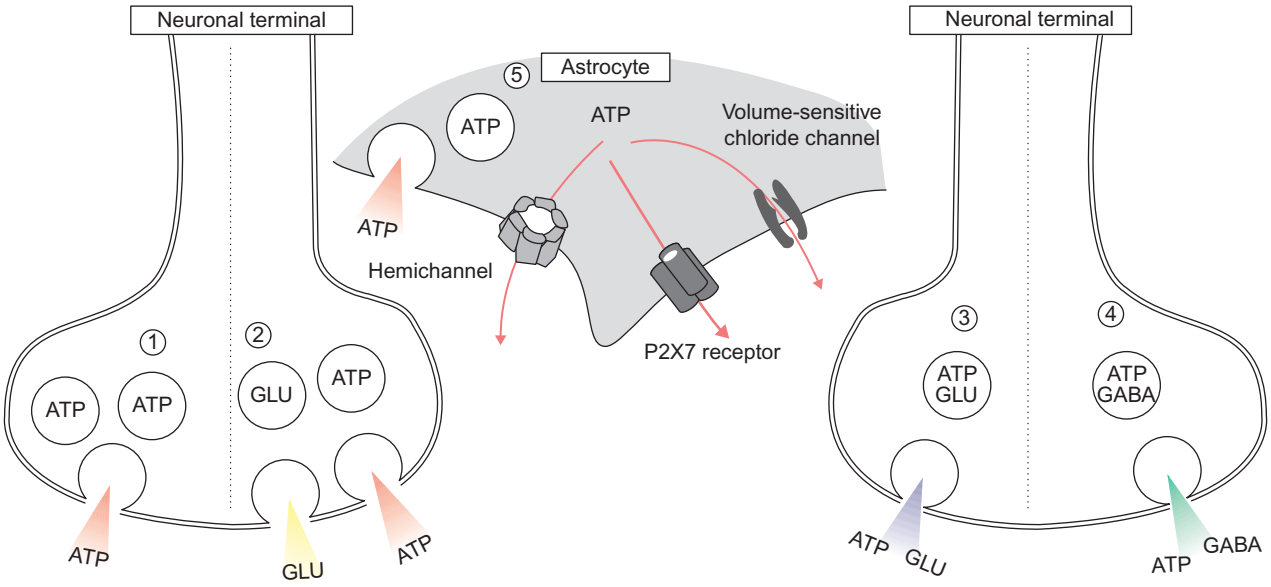

FIGURE 16.36 The energy molecule ATP is also a neurotransmitter. *Source*: Verkhratsky and Krishtal in Squire, 2009.

make it easier to remember the dizzying dance of molecules in the brain. One great source of simplification is the fact of reutilization of basic life molecules for the purposes of running the brain.

Figure 16.36 shows another example, the case of the energy molecule adenosine triphosphate (ATP), which is utilized in every cell in the body. ATP also functions as a neurotransmitter, sometimes in collaboration with glutamate or GABA, and always with the aid of glial cells, in this case the astrocyte.

5.9 Cleaning up the synapse: deactivation, diffusion, recycling

Regulating the concentration of bodily chemicals is crucial. We depend upon the right amounts of the right molecules for survival, and can develop disease due to overproduction or underproduction. All chemical reactions in the body produce some free radicals, fractions of molecules that carry an extra plus or minus charge. Among the most common are reactive oxygen species such as H_2O_2 and OH-, but also protein fractions like the amine fraction of amino acids. Because they are charged particles these charged molecules can do a great deal of damage, since they can interact with any other particle with opposite charge. Their action is sometimes called 'cross-linking' – the cause of wrinkling of the skin by uncontrolled making of random links. Such constant, random reactions are a major factor in aging and age-related diseases like atherosclerosis. To defend against free radicals the body has a large collection of antioxidants that can 'mop up' reactive species, including vitamins and certain oils.

Similarly, the physiological response to injury is inflammation, a complex cascade of cellular and molecular events that is vital for healing. However, chronic inflammation is also a major factor in degenerative diseases, including neurodegenerative disorders like Parkinson's and Alzheimer's disease. Again, the regulation of chronic inflammation is essential for maintaining a healthy nervous system.

The brain is the most energy-intensive organ in the body, certainly under modern living conditions, when most human beings are not walking or running during the day. The brain therefore generates a large concentration of free radicals and potential inflammatory events. The synapse and the extracellular space are two locations that are vulnerable to a loss of chemical control because they are not embedded in the self-regulation machinery of the cell (which develops its own degenerative events over time, however).

Cleaning up the synapse is a good illustration of the general need to control the buildup of toxic molecules. We have already mentioned that glutamate, the most common neurotransmitter in the brain, becomes toxic if it is not removed from the synapse quite rapidly. Excitotoxicity (glutamate toxicity) is the most common cause of brain damage after a stroke, a surprising finding. A stroke involves the rupture of a blood vessel in the brain. But the primary effects of blood seeping

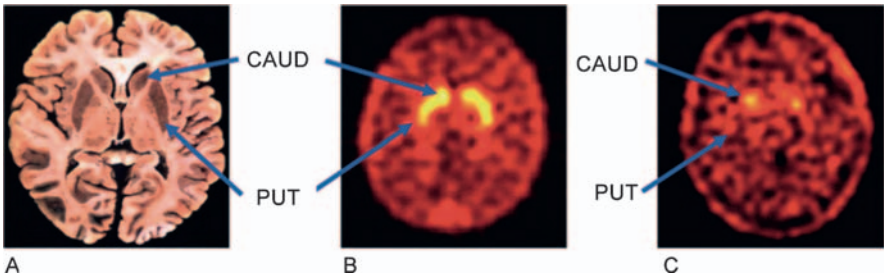

FIGURE 16.37 Transporters recycle dopamine back to the source. Axial SPECT images of a radioactively tagged dopamine transporter molecule. The caudate nucleus and putamen (basal ganglia) are labeled. The left image is an anatomical slice of a human brain post-mortem, to illustrate the level of the section. The middle image shows a normal brain, with high levels of the radioactive signal in the caudate and putamen. On the right is the corresponding image in a patient with Parkinson's disease, which is caused by a loss of dopamine neurons in the substantia nigra (SN), which project their dopaminergic axons over wide regions of the forebrain. The basal ganglia are modulated by SN neurons involved with motor control, one of the major deficits of Parkinson's disease. *Source*: Newberg and Alavi, 2009.

outside of the circulatory system, and perhaps tearing and disrupting other tissues, are less harmful than the subsequent damage due to free radicals, inflammation, and excitotoxicity. The treatment for stroke has therefore shifted toward treating the secondary effects of stroke, which begin immediately after a blood vessel ruptures.

The nervous system has evolved a number of ways to keep the concentration of potentially harmful molecules in the synapse under precise control. The three general types of synaptic 'clean-up' are:

1. *Diffusion* of the neurotransmitter molecule, which is typically the case for the gas-state neurotransmitter nitric oxide (NO). NO was not known to be a neurotransmitter until the past decade or so, but has since turned out to play a major role at many synapses, including perhaps the most famous example, its use in Viagra. However, NO has many other functions in the nervous system. Because it is a gas, and is secreted rapidly in very small quantities, it diffuses safely out of the synapse very quickly.
2. *Degradation*. Acetylcholine is degraded by the enzyme acetylcholinesterase (*-ase* is the general suffix for deactivating enzymes). Enzymatic degradation may occur by literally cutting the neurotransmitter into smaller pieces, something that is often possible with long protein molecules. The components can then be recycled into the presynaptic neuron.
3. *Recycling* or 'transport' of the neurotransmitter back to the source neuron. Dopamine is perhaps the best-known example of a recycling neurotransmitter. Figure 16.37 shows a SPECT scan using a radioactively tagged molecule attached to the dopamine transporter molecule. The brain on the left is an anatomical slice post-mortem; the middle photo is a SPECT image of a normal subject, showing high concentration of the dopamine transporter, especially in the basal ganglia and thalamus (caudate nucleus and putamen); and on the right side, a SPECT scan of a Parkinson's patient with impaired dopamine production. The last image has lower levels of dopamine transporter, probably reflecting the lower levels of dopamine in the patient's brain. However, it is possible that Parkinson's disease disrupts the dopamine transporter in some more direct way.

6.0 NEUROMODULATORS

Neuromodulation differs from neurotransmission in that signaling molecules are very widely distributed through parts of the brain. The same molecule may play two different roles, depending on where it is secreted. Acetylcholine and glutamate can either be neurotransmitters or neuromodulators. As neuromodulators they modify large swaths of brain territory by regulating local synaptic signaling among billions of neurons and synapses. For example, neuromodulators may change the baseline membrane voltage of a population of cells, and thereby modify their local synaptic signaling. By switching neuromodulators between waking, sleep, and REM dreaming, the brain can control the balance between sensory input versus internal processes, for example. In waking, sensory signals

flow freely, but they may be blocked or turned down during slow-wave sleep and REM. The difference is controlled by the widespread neuromodulation of those states.

Neurotransmission is usually faster than neuromodulation, and is more likely to be ionotropic, while neuromodulation is slower and more likely to be metabotropic. Notice also that multiple neuromodulators might be switched on at the same time. The waking state, for example, is 'turned on' when acetylcholine, serotonin, norepinephrine, and dopamine, among others, simultaneously begin to be distributed in overlapping regions of the cortex and thalamus (see Chapter 8). Table 16.2 shows why the brain needs to have multiple capacities enabled at the same time during the waking state, capacity being enabled by a different neuromodulator: such as alertness *along with* motivation, *plus* sensory clarity (high signal-to-noise ratio), *plus* accurate planning and motor control. During waking we want to use all of those interacting capacities as needed.

Neuromodulating nerve cells typically are located in small clumps near the bottom of the brain – in the brainstem or the basal forebrain – where they 'spray' their messenger molecules over large tracts of the forebrain (Figure 16.39). The conscious waking state is turned on by neuromodulators such as acetylcholine, norepinephrine, and dopamine. Together, they enable a huge repertoire of different cognitive tasks. Each of those tasks involves a combination of local neurotransmitters like glutamine and GABA, along with neuromodulators that control the overall brain state that is needed for a task like perception or working memory to take place.

Thus the substantia nigra (SN, literally the 'dark substance' in Latin) is a small wedge of nerve cells located just above the brainstem, which send their axons spreading upward to modulate the activity of billions of other neurons (Figure 16.38). The SN has about 10 000 *dopaminergic* neurons, not many compared to the tens of billions in the cortex. But their influence is huge – and correspondingly, when dopaminergic SN neurons are lost, as in Parkinson's disease, the loss can be very serious. Dopamine modulation is involved with basic functions like pleasure and reward seeking, sleep and waking, nicotine and stimulant addiction, working memory, voluntary motor control, eye movements, and goal-directed learning. It is a huge set of functions. (Like other brain structures all neuromodulating nuclei come in pairs, one on each side of the brain. Each SN has two distinct regions, called pars compacta for the 'dense part,' and 'pars reticulata' for the 'network-like part.')

Most synapses *combine* local transmission with regional neuromodulation. For example, a visual neuron in cortex might behave quite differently depending on global brain states, like sleep or waking, which are controlled by brainstem nuclei that project their axons

TABLE 16.2 Major neuromodulator functions

Neuromodulator	Some major functions
Norepinephrine	Maintains high signal-to-noise ratio in sensory systems
Serotonin	Protects from information overload and reduces cross-talk between different sensory channels
Biogenic amines and acetylcholine:	
Dopamine	Maintains psychomotor and motivational focus and alertness (conscious arousal)
Acetylcholine	Mediates attention and conscious arousal (waking and alertness) in all sensory systems
Beta endorphin	Counteracts homeostatic imbalances; enables pleasurable feelings
Corticotropin releasing factor (CRF)	Promotes the effects of stress and negative emotional stimuli
Neuropeptides	
Vasopressin/oxytocin	Vasopressin promotes male-type persistence; oxytocin promotes female-type nurturance and acceptance
Cholecystokinin	Regulates emotional system, feeling, sex, exploration, and pain

Source: Northoff and Panksepp, 2008.

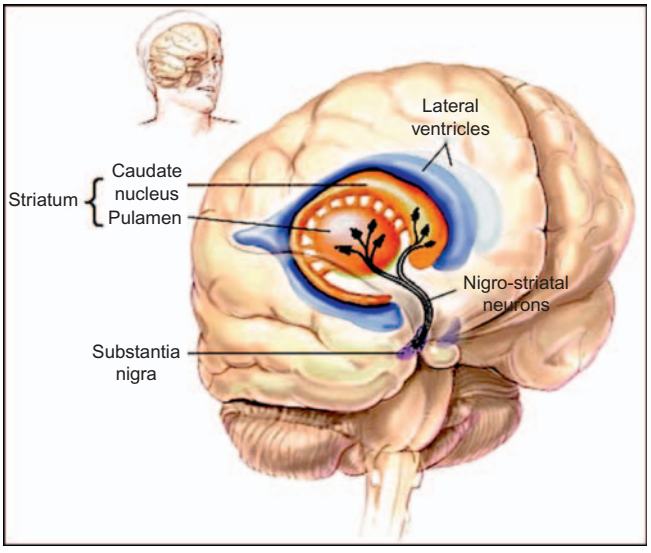

FIGURE 16.38 Neuromodulation: basal brain nuclei shape widespread brain functions. Neuromodulation from small nuclei in the basal brain shapes the general activity of the cortex and basal ganglia. *Source*: National Institute of General Medical Sciences, 2009.

to cortex, distributing neuromodulator molecules like acetylcholine and dopamine far from their cells of origin.

7.0 LEARNING

Chapter 9 covered learning and memory at the large scale of the brain. Here we will explore some of the molecular aspects, which have been studied very intensively in the past few decades. Scientific progress in this field is likely to have great impact, not just in coping with learning disorders, but in greatly improving learning over the lifetime.

All brain regions are involved in learning, memory, and plasticity, which can be considered as different methods for evoking long-lasting adaptive changes in the brain. The most typical example of such adaptation is believed to be Hebbian learning, defined as the growth of synaptic connectivity due to coordinated neuronal firing. The slogan for Hebbian learning is that 'neurons that fire together, wire together.' That is a good first approximation to the neuronal level of learning. The major point here, however, is that this fundamental kind of learning might be observed almost anywhere in the brain where two neurons join at a synapse. Figure 16.40 shows the wide range of learning processes that are known to occur, along with the brain regions that support them. There is no *single* learning region of the brain. All brain functions can adapt to changing conditions. The sensory (posterior) half of the cortex adapts to changing sensory conditions, most famously in early visual learning in kittens (Hubel and Wiesel, 1968). An everyday example is our growing experience of a new variety of music or art, where simply paying attention to the song allows for a deeper and often more satisfying experience of the same physical event.

The frontal half of cortex supports the learning of executive functions (Chapter 12), working memory, speech and language-related learning, and of course motor control. Merzenich and coworkers (1984) showed that the loss of a single finger will cause an adaptive reorganization of the hand and finger maps in cortex. Whereas previously all five fingers were well represented (as shown by stimulation of the fingers, with corresponding activity recorded from the cortical finger maps), after amputation the cortical map lowered its responding to the missing finger and increased the representation of the remaining

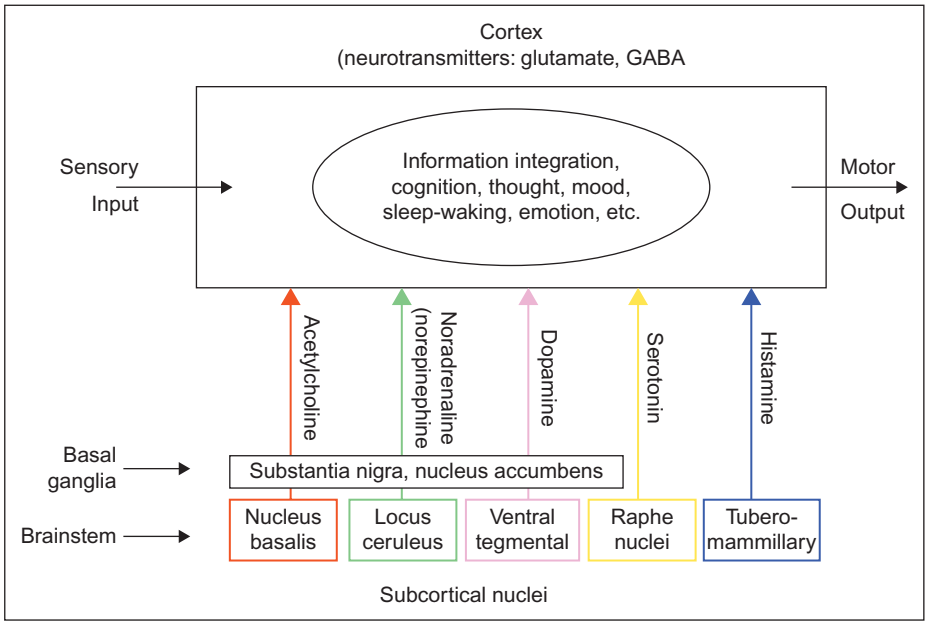

FIGURE 16.39 Five major neuromodulators. Notice that all of these neuromodulators project axons from small nuclei below the cortex, spreading their neurochemicals to wide regions, both cortical and subcortical. Only a few thousand cell bodies in these nuclei therefore have massive effects in the rest of the brain, controlling sleep and waking, pleasure and pain, alertness and working memory. When neuromodulating cells die off, as in the case of dopaminergic cells in Parkinson's disease, the results can be debilitating and ultimately deadly. *Source*: Adapted from Gu, 2002, Figure 1.

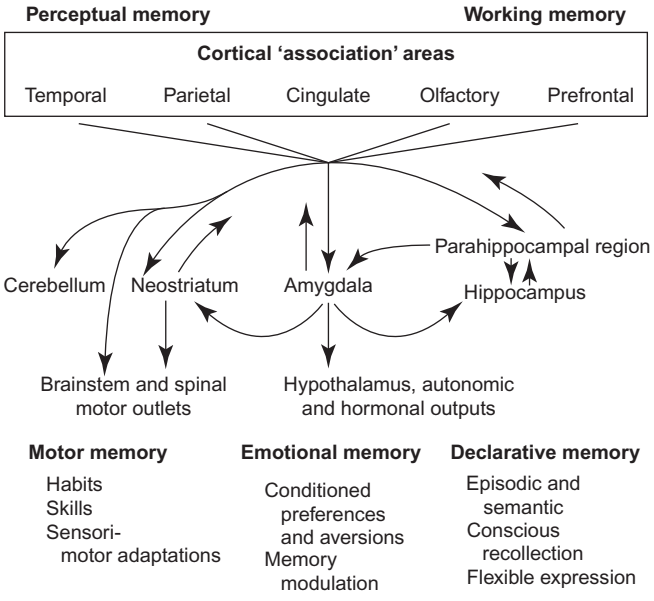

FIGURE 16.40 Learning occurs everywhere in the brain. Memory storage occurs in the same regions that are used in active tasks. Thus perceptual memory appears to involve selective strengthening and tuning of synapses and receptive fields in the perceptual half of cortex. The amygdala, hippocampus, and medial prefrontal lobe are involved in different aspects of emotional learning. Declarative memory (i.e. memory for conscious episodes and concepts) is mediated by the hippocampal complex, but after consolidation, declarative memories are also stored in the neocortex (see Chapter 12). Thus learning of one kind or another occurs in all parts of the brain. *Source*: Eichenbaum, in Squire, 2003.

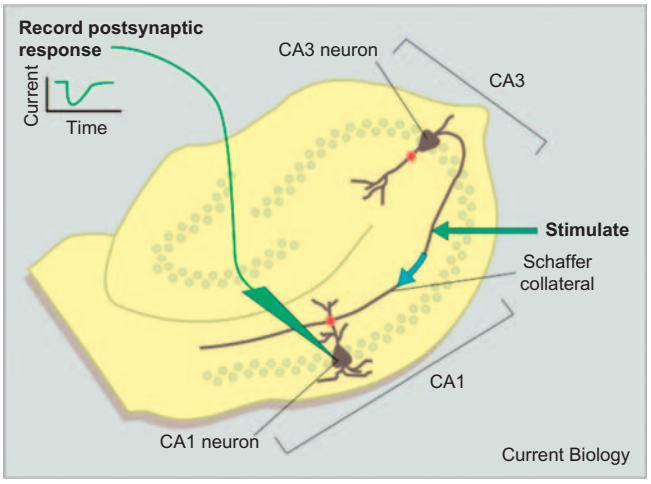

FIGURE 16.41 A hippocampal slice culture. This slice of hippocampus can be kept functioning in culture, allowing experimenters to apply different neurotransmitters and record from different kinds of neurons at the same time. While the typical hippocampal slice is rat tissue, it has striking similarities to human hippocampus. The figure shows three types of hippocampal neurons, CA1, CA3 (named after the Cornis Ammonis, the curved section of hippocampus that looks like a horn), and Schaffer collaterals. *Source*: Stevens and Sullivan, 1998.

neighboring fingers. Thus cortical representation was optimized for the working fingers. This is a general principle that applies to all sensory and motor regions of cortex, and probably to prefrontal regions as well (Merzenich *et al*., 1984).

A similar reduction of cortical finger map size occurs when we use one finger repetitively. When the same finger movement is repeated over and over again, the cortical representation of that finger will decrease, as if the cortex is treating it as a redundant (highly predictable) event. However, subcortical innervation of the finger does not disappear, because the brain is still controlling and monitoring finger movements.

7.1 The hippocampal complex

Declarative memory for conscious events seems to primarily occur via the medial temporal lobe, what we have called the hippocampal complex (because it is broader than just the hippocampus by itself). Chapter 8, Figure 8.16, shows a dynamic circuit for the temporary storage of conscious episodes during the waking state, including the sensory cortex, thalamus, and the hippocampal complex. Keep in mind that a great deal of episodic learning also engages implicit circuits, so that conscious cues normally carry their own implicit (unconscious) sequelae, which must also be encoded in the brain. A well-studied example is the role of word sequence learning in children, and the implicit induction of grammatical rules and regularities as a result of explicit learning. A three-year-old child may say *'Mommy, airplane!'* but the implicit expression is richer than those words. It implies, 'Mommy, pay attention to me, and look there, where I'm pointing, where there is an airplane going over in the sky.' That implicit knowledge must also be learned, both by mother and child. There is likely to be no such thing as *isolated* explicit learning; all explicit cognition also has an implicit side to it.

Episodic learning is well established to take place in at least two stages, the first one lasting on the order of seconds, minutes, and hours, and involving the hippocampal region (MTL), which receives input from vision and the other senses (see Figure 16.41 for a typical hippocampal slide preparation). In the case of vision, for example, the temporal lobe involves the integration of different visual feature streams into coherent objects and events. It is those conscious objects and events that become the contents of immediate memory. See Figure 16.42 for a cross sectional slice of the hippocampus showing the great complexity and

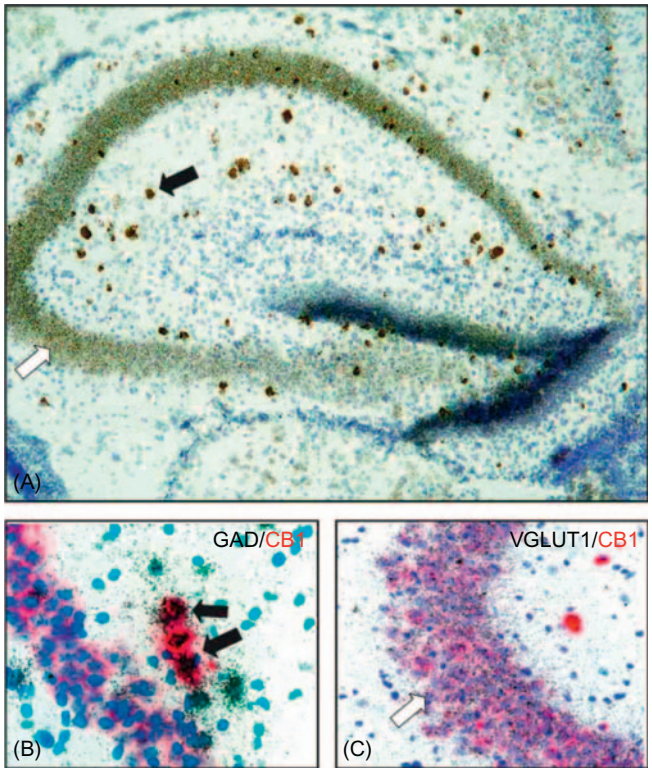

FIGURE 16.42 Endocannabinoid activity in the hippocampus. Endogenous cannabinoid molecules are important in learning and synaptic plasticity. (a) This photograph of a cross-section of the hippocampal formation uses *in situ* hybridization to color stain the different tissues. The brown colors indicate CB1 receptor mRNA. Cell nuclei are stained blue. GABA-ergic neurons are shown by the black arrow and glutamatergic pyramidal cells with the white arrow. (b) shows the co-expression of CB1 receptor mRNA (red) with a GABA marker (GAD). (c) shows the co-expression of the CB1 receptor mRNA (red) with a molecular marker of glutamate transporter type 1 (VGLUT1). Notice the great complexity and richness of the molecular coding involved in hippocampal learning. *Source*: Lutz and Marsicano, in Squire *et al*., 2009.

richness of the molecular coding involved in hippocampal learning. Those memories are labile (unstable), so that they are vulnerable to interference. An electrical shock delivered soon after learning will disrupt new memories but not old and stable memories.

The traditional question is what molecular and cellular events cause long-term memories to be established. However, it now appears that even immediate memory, the dynamic circuit shown in Figure 8.11, also involves molecular and epigenetic activities. We will explore this point later (Wang, 2003).

7.2 Glutamate, GABA, LTP, and LTD

If learning involves making connections between neurons, conceptually we can have two types: either an increase or decrease in the event probability of the link. Traditionally this has been called long-term potentiation (for strengthened links) and long-term depression (for weakened links). They correspond conceptually to excitation and inhibition, although the electrochemical mechanisms are not identical. In fact, over decades of efforts to identify the brain basis of LTP and LTD it has become clear that there are many mechanisms of LTP and LTD in the brain, just as there are many varieties of neurons, synapses, neurochemicals, and so on. Nature thrives on a diversity of means, using many different ways to accomplish the same fundamental functions. One reason for the vast diversity of pathways and mechanisms at all levels of biological organization is that functional redundancy leads to stability in the face of changing conditions (Edelman & Gally, 1992). Human engineers also use multiple backup systems in complex projects to ensure continuity of functioning if something goes wrong.

Figure 16.43 shows how LTP and LTD can be studied in hippocampal slices, and in many neural preparations. The stimulus in this case is labeled 'tetanus,' a small electrical shock. The vertical axis shows millivolts per milliseconds, as an index of neuronal membrane voltage over time. That level roughly doubles immediately after the tetanic shock and continues at a high level for more than 90 minutes. It is the duration of the higher activity level that suggests that we are not dealing with excitatory or inhibitory neural transmission but with a longer-term change in the neuronal circuit.

7.3 Glutamate synapses as early models of synaptic learning

The first LTP system to be studied in detail was the glutamate synapse, by far the most common excitatory synapse in the brain.

Figure 16.44 shows an example of Pavlovian conditioning in one of the best-studied organisms in biology, the fruit fly, *Drosophila melanogaster. Drosophila* is quite a smart creature, with as many as 100 000 neurons in its brain. It is a skilled flyer, pathfinder, pattern-recognizer, learner, and social creature – with male-male aggression in competition for a female or food, and sexual selection for the most suitable partner for reproduction. Olfaction is one of its developed senses. Odors like the scent of fruit sugars can guide the fly to food, warn it away from toxins, and serve as pheromones to attract it to the opposite sex. The fruit fly can learn to associate an arbitrary odor with an aversive

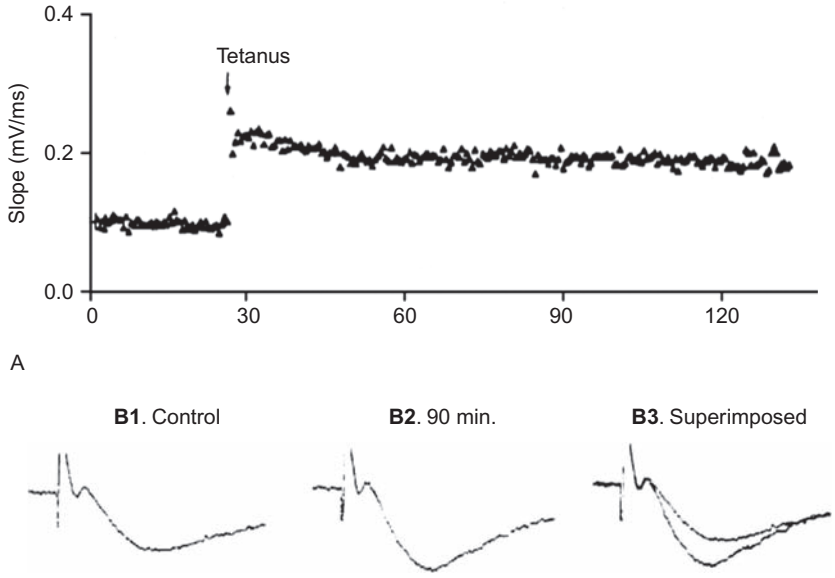

FIGURE 16.43 Measuring long-term potentiation (LTP) and long-term depression (LTD). Notice that this figure shows only the input (tetanus shock) and output (millivolts per milliseconds) of the preparation. In the case of a hippocampal slice culture we may be seeing the activity of a single synapse or of entire connected layers of neurons (like CA1, CA3, and the Schaffer collaterals). *Source*: Byrne, in Squire *et al.*, 2003.

event, like a shock, because electrical tetanus (shock) triggers signaling in all neural tissues. Neurons communicate electrochemically and are therefore sensitive to electrical pulses. Shock can also be painful and aversive, activating neural circuits for harm detection and avoidance.

Figure 16.44(a) shows the experimental apparatus, a small T-maze for the fly, baited with two end boxes with two different odors. Odor 1 serves as the conditioned stimulus, the arbitrary signal for the unconditioned stimulus, the electrical shock to the fly's legs as it is walking through the horizontal plastic tube. When Odor 1 is followed by shock to its legs, the fly quickly learns to go in the direction of the safe odor, Odor 2, and stay away from Odor 1 at the choice point in the T-maze. A stream of air helps to move the fly along, and keeps it from going back to earlier points in the maze.

Figure 16.44(b) illustrates how associative learning is believed to occur at glutamate synapses in *Drosophila*. The theoretical question is simple, and straight from Donald Hebb: If the two neurons fire together, will they wire together? Will the chemical synapse be able to detect events that go together, like Odor 1 and the electrical shock? And can the synapse be strengthened and made more likely to go into action the next time Odor 1 is encountered? The question may seem simple, but the molecular machinery needed to do the job is not trivial (see Figures 16.45, 16.46, and 16.47 for schematic illustrations of how this occurs). What's more, there is good reason to think that the glutamate synapse that supports learning in *D. melanogaster* is highly conserved among other species, including human beings.

One interesting way to strengthen synaptic links between two neurons is to literally tie the two cells together, using cell adhesion molecules. Figure 16.48 shows how this works in concept.

Learning always requires structural changes in neurons – growing dendritic spines, making new synapses, and building up the metabolic machinery to sustain higher rates of neuronal activity. A great deal of learning is believed to involve the Hebbian growth of connections between neurons, following the rule that 'neurons that fire together, wire together' (Chapters 3 and 10). Since 'wiring together' requires growing bigger and more interconnected neurons, epigenetic control of protein expression becomes an essential part of the story. By definition, learning involves 'experience-dependent changes in the brain.' The experiences we have during our waking hours constitute environmental input, and the resulting brain changes require new

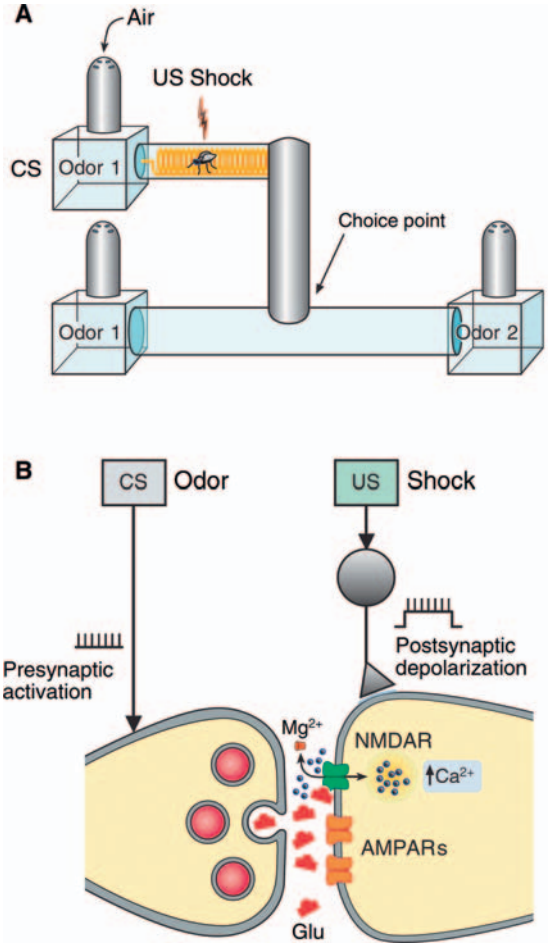

FIGURE 16.44 Pavlovian learning in the fruit fly. Classsical conditioning in the fruit fly allows the study of associative learning in a relatively small nervous system, using fear conditioning of an arbitrary odor to signal an electrical shock. The two ionotrophic receptors for glutamate are NMDA and AMPA (the R stands for Receptor). They directly open ion channels in the target membrane, including calcium and magnesium channels. Notice the firing rate of the two neurons (marked by a 'comb' shaped set of vertical lines). Long-term potentiation requires additional changes deeper in the cells, to enable structural changes in the synapse. *Source*: Glanzman, 2005.

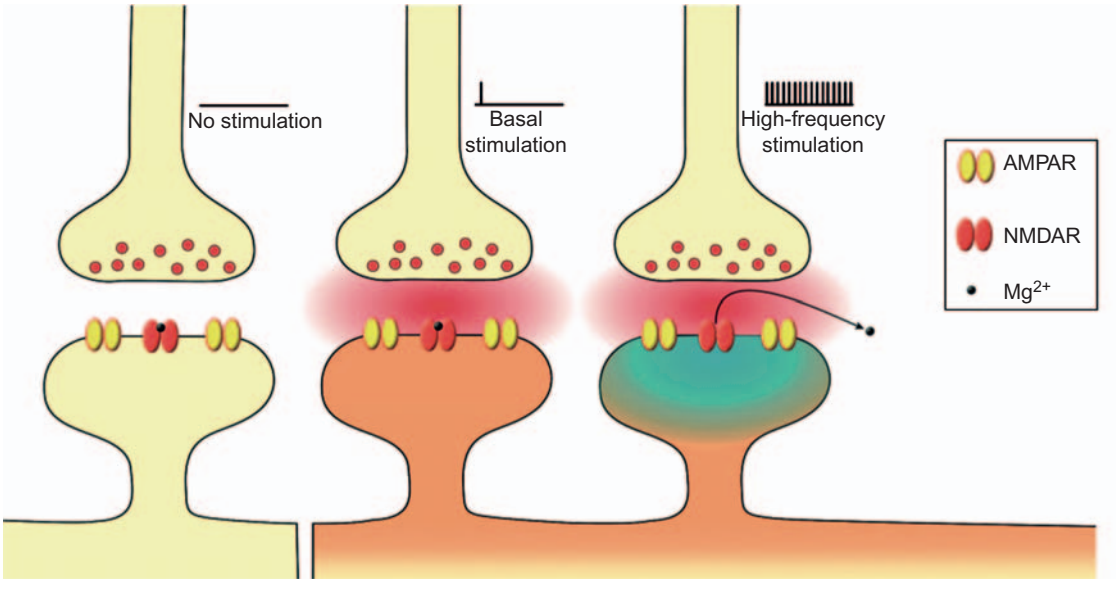

FIGURE 16.45 Long-term potentiation using NMDA and AMPA receptors. A closer look at the firing-rate dependency of the NMDA receptor for LTP. On the left, in the absence of glutamate transmission across the synapse, NMDAR is blocked by magnesium ions (small black dot). The center figure shows the same synapse at the basal firing rate of the presynaptic cell, the background rate that does not signal any particular event. Glutamate (red) diffuses across the synaptic gap, but the NMDA receptor is still blocked by the magnesium ion. On the right, high-frequency signaling from the presynaptic cell triggers the NMDA receptor. Thus the synapse operates as a high-bandpass switch that opens only when provided with a high-frequency input. *Source*: Doherty, Fitzjohn, and Collingridge, in Squire *et al*., 2009.

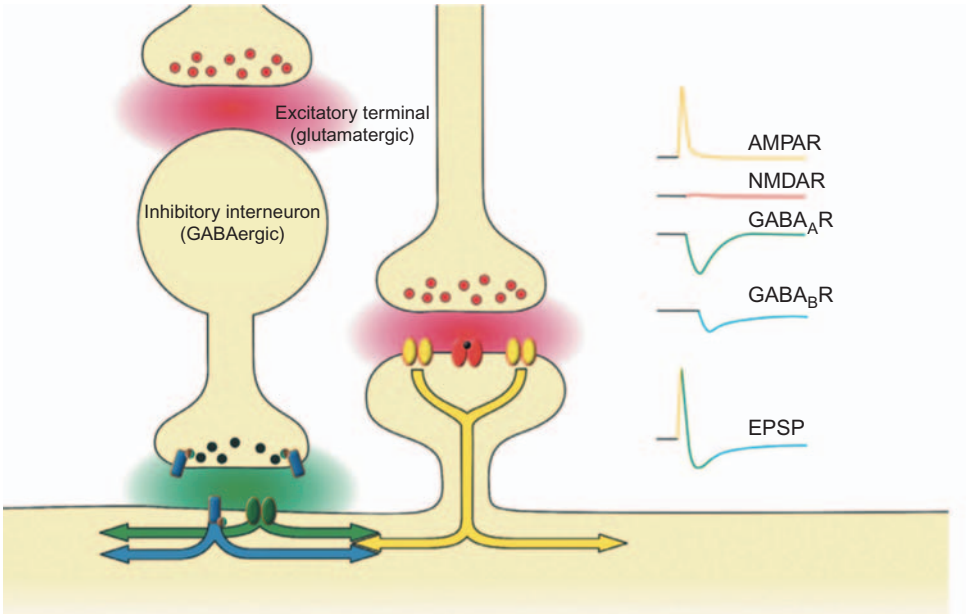

FIGURE 16.46 Long-term potentiation: a closer look at NMDA. Learning is not limited to single neurons. Rather, it is usually a network event, involving multiple excitatory and inhibitory synapses. In this case, on the top left, an excitatory (glutamatergic) cell innervates an inhibitory cell (GABA-ergic), which in turn lowers the firing probability of the target cell at the bottom of the figure. Thus the target cell receives both inhibitory and excitatory inputs. On the right side, the membrane voltages due to GABA and glutamate are added, with the AMPA receptor yielding a positive spike and the NMDA receptor being blocked by a magnesium ion (black dot). Two GABA receptors are represented, GABA (A) and GABA (B), with slightly different effects on the target cell. The EPSP (excitatory postsynaptic potential) is the 'bottom line' of the system, which yields a spike followed by a refractory period. Circuits like this can become quite complex and adaptable. *Source*: Doherty, Fitzjohn, and Collingridge, in Squire *et al*., 2009.

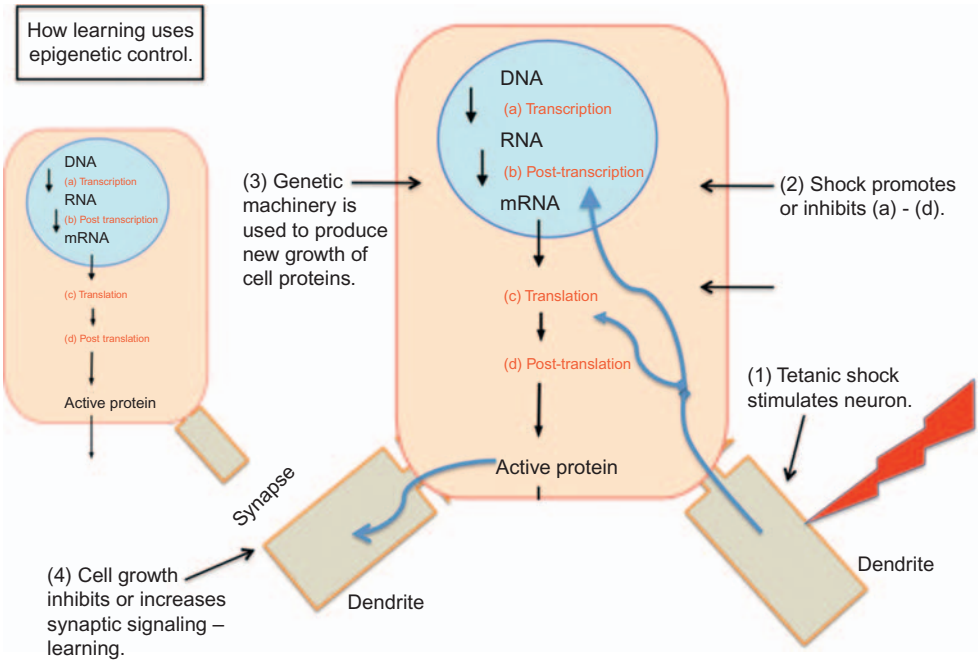

FIGURE 16.47 Translational and transcriptional activation for LTP/LTD. LTP and LTD require protein synthesis to grow the number of synapses, add synaptic spines, and increase the flow of neurochemicals (typically proteins) to all parts of the system. When a synapse is strongly stimulated both translational (mRNA) and transcriptional (DNA-mRNA) mechanisms are activated.

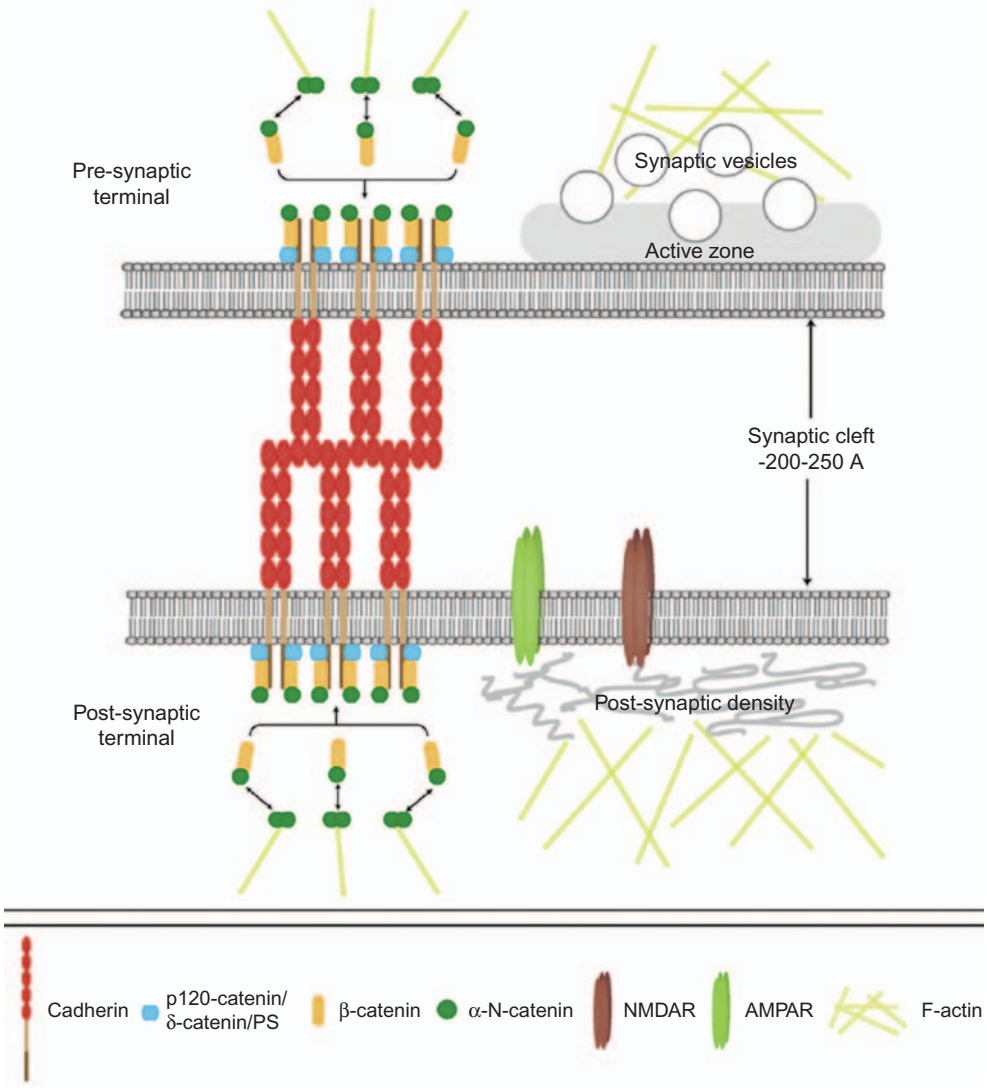

FIGURE 16.48 Cell adhesion molecules stabilize the synapse. The red cadherin proteins work to keep the two neurons at the synapse together, thereby facilitating neural signaling across the synapse. Cell adhesion molecules have numerous functions, and seem to be essential for learning and plasticity. *Source*: Tai, Kim, and Schuman, 2008.

bricks and mortar to permit active neuronal networks to adapt to those daily encounters with the environment. Like an automobile factory, each cell responds to adaptive demands by making more of a variety of different products (see Figure 16.49).

We have described learning in Hebbian terms, as the strengthening of synaptic links among neurons. That picture is correct as far as it goes, but it is only part of the adaptive apparatus of the living brain. It is believed that there may be non-Hebbian learning mechanisms as well. Adaptation to the world, to ourselves, and to each other, is after all what the brain *does*. Given hundreds of millions of years of evolution, brains have evolved many mechanisms of adaptation; they all involve 'learning' in a broad sense of that word. The terms 'learning,' 'memory,' and 'neural plasticity' have now become near synonyms. Historically, the term learning was influenced by the associative learning tradition, particularly for Pavlovian and operant conditioning. Plasticity was first studied in the realm of perceptual learning, such as Hubel and Wiesel's seminal work on the adaptation of occular dominance columns in kittens that were deprived of input to one eye or the other. Plasticity was studied in terms of *imprinting* during *critical periods*, the rapid learning that takes place in a restricted period of time in young mammals, and perhaps in the fetus even before birth. Imprinting during critical periods is key to the early growth of

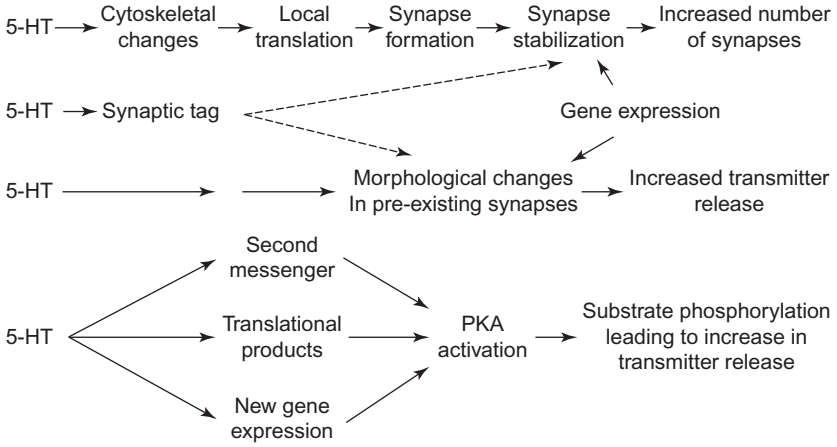

FIGURE 16.49 Some ways for synaptic signaling to be strengthened. There are multiple ways to increase synaptic strength. In the case of serotonin (5-HT) this table suggests four different ways. One is a change in the structural supports of the cell, the cytoskeleton, including an increased number of synapses. Serotonin can also evoke a synaptic tag, triggering gene expression to support greater synaptic stabilization. (Synapses, like other cellular elements, are constantly cycling and having to be replenished.) The neurotransmitter can also make morphological changes in pre-existing synapses, enlarging them, or adding to the flow of molecules diffused across the synaptic cleft. And finally, serotonin can work via a second messenger like a G-protein, enhance translational productions (involving mRNAs), or new gene expression (by epigenetic changes in DNA expression), leading to a cascade resulting in greater transmitter release. *Source*: Sossin, 2008.

the visual brain, for example, to visuomotor learning, speech perception and production, and much more.

But the term plasticity has greatly broadened in meaning. Adults are now known to have cortical plasticity throughout the lifetime, even if it is less dramatic than the early plasticity of the visual brain. Major changes in the sensory or motor domain, such as the loss of a finger, trigger immediate plasticity in the allocation of neurons in the sensorimotor cortex. But even simply practicing a repetitive movement, as in typing the same keystroke, will also trigger reassignment of the cortical map for that finger, and for the neighboring fingers. Thus 'plasticity' is merging with other labels for the adaptive function of the nervous system. Sometimes it is useful to emphasize the differences, but we will treat them as parts of the same topic.

Memory, as a technical term, has its own scientific history, with an emphasis on the nature of stored representation. But there is a tendency to use those words interchangeably when it comes to the brain basis. One reason is that it is hard – perhaps impossible – to find truly different brain events corresponding to the traditionally separate terms.

The brain begins learning as soon as it is placed in any novel environment – which is any environment at all. New stimuli tend to trigger a massive orienting response, including widespread brain activation. When the animal feels safe enough to explore the novel environment, it will begin to gather information by sniffing and looking. Simple novelty is enough to trigger attention and learning, including significant evoked potentials that sweep through the entire cortex.

A rodent in a laboratory task is acutely sensitive to the experimenter's personal odors, for example, such as the odor of the experimenter's pet cat. To a laboratory rat the predator odor signals imminent threat, and some researchers report a tendency for rodents to hunker down in fright. Learning is hardly optimal under those conditions or, rather, the animal is learning something different from what the experimenter thinks it is. Learning of experimental tasks usually requires the animal to feel safe enough to explore.

In the real lab, as in real life, animals are doing all kinds of learning at the same time. When we look at brain events, that rich set of adaptive processes becomes apparent.

7.4 Epigenetics of learning

As mentioned before, epigenetics has now become crucial to the study of learning. That is, learning engages the genetic controls for the neurons and glia that are engaged by the task. Neurotransmitters alter

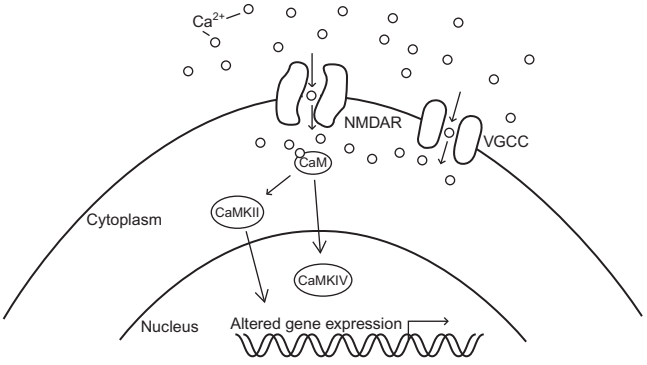

FIGURE 16.50 Activity-dependent gene expression (CaMKs). *Source*: Nelson and Monteggia, in Squire, 2009.

the DNA expression of their cells of origin and their target cells. Since DNA encodes the control plan for the production of molecules, including neurotransmitters, this makes sense for the presynaptic cell. But it is equally true for the postsynaptic cell, and for neighboring glia as well.

Figure 16.50 shows activity-dependent gene expression in a postsynaptic cell. Rhythmic stimulation of neurons evokes specific gene expressions that enable learning to occur. Theta rhythms are known to occur with episodic learning in the hippocampus, and later on, as a vehicle for hippocampal-neocortical memory consolidation. Thus theta may have the effect of changing the very nature of the neurons it recruits. Such rhythmic stimulation also triggers epigenetic processes in cell populations.

This particular mechanism makes use of very important calcium-dependent molecules called CamK (for calmodulin-dependent kinase), which help to induce plasticity by altering gene expression in the nucleus. As Figure 16.50 shows, calcium ions flow into the cell when the NMDA receptor opens the channels (along with voltage-gated calcium channels). The rise of calcium ions binds to the protein calmodulin (CaM), which activates proteins involved in the regulation of gene expression.

Brain molecules are prime targets for drugs to improve mood disorders, dementia and stroke, brain injury, sexual functioning, coma, attention and memory, insomnia, daytime sleepiness, and more. Add a range of recreational and addictive drugs – often with negative or simply unknown safety profiles – hormones, heavy metal toxins, steroids, and the like, and we seem to be living in a world of brain-targeting chemicals. A newer category of pharmaceuticals, called *nootropics* (from the Greek words for mind, *nous*, and *tropos*, movement), aims to improve our ability to learn and stay alert. Some time in the future college students are likely to go beyond drinking lots of coffee before an exam to use safe and effective nootropics.

7.5 Neurotrophic factors in learning

In learning to play guitar our spinal motor neurons may need structural strengthening. For building bigger neurons with longer branches we need to recruit cellular growth mechanisms called neurotrophic factors (Figures 16.51 and 16.52). One of those is a molecule called BDNF (for brain-derived neurotrophic factor). Recent evidence shows that BDNF injected into the brain vesicles of rodents improves their learning, and that BDNF injections also increase slow-wave sleep. That is consistent with the evidence that SWS plays a role in memory consolidation, enabling structural changes for long-term memory (Chapters 8 and 9).

8.0 SUMMARY

In this chapter, we have discussed how basic life molecules – such as glucose, choline, and calcium – are also used for neural signaling in the brain. These 'molecules of cognition' serve to carry brain signals that enable us to perform our everyday tasks. Life uses *enzyme* chemistry, making constant use of molecular nanomachines that speed along a second-by-second flow of chemical reactions. All brain chemicals act enzymatically. The life molecules are highly conserved, by which we mean that they are found across many species. Importantly, these molecules may perform differing functions depending on whether they are acting in the body or the brain.

All human cells have a complete copy of our species genome in their nuclei, in the form of a long, linear DNA code, twisted into the well-known double helix. The genetic code is *expressed* in proteins that define, develop, regulate, and control the phenotype. In each cell nucleus DNA is *transcribed* into messenger RNAs, which then are *translated* into proteins. The Central Dogma of molecular biology claims that that molecular causality flows *from genes to messenger RNA to body proteins*, but not the other way around.

Genes and molecules play different roles in different stages of development: they shape the evolution of the brain, such as the frontal lobes – including language, social relationships, and the ability to recognize facial expressions. They control the program for lifelong brain development, from fetal growth to

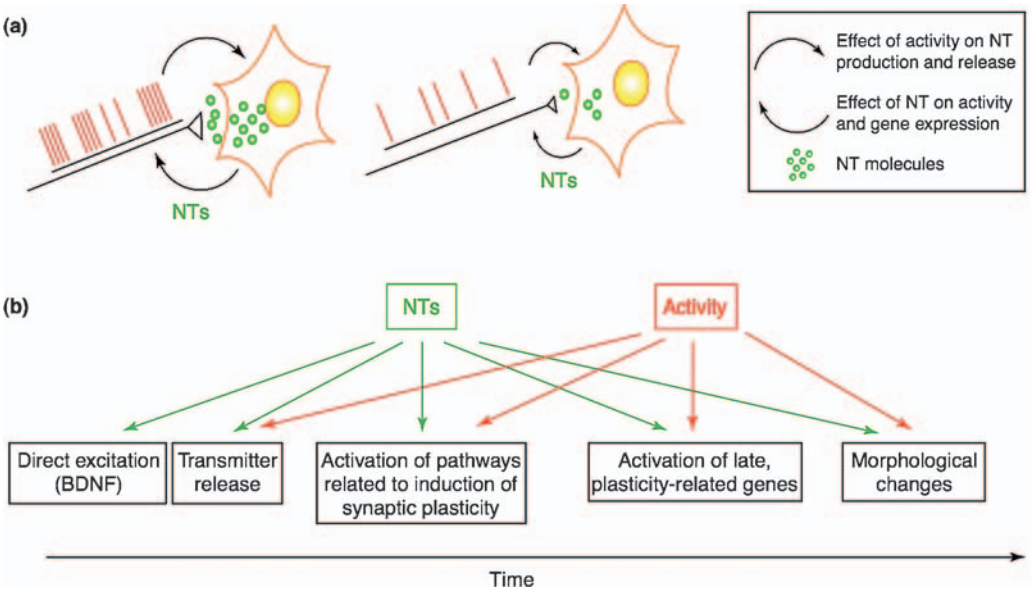

FIGURE 16.51 Growth factors in learning. The body is constantly maintained by molecules called growth factors, such as human growth hormone. Two growth factors are also important in learning, called neurotrophin and BDNF (for brain-derived neurotrophic factor). Neurotrophin is driven by the firing rate of neurons, and by the flow of neurotransmitters across the synapse. *Source*: Berardi *et al*., 2003.

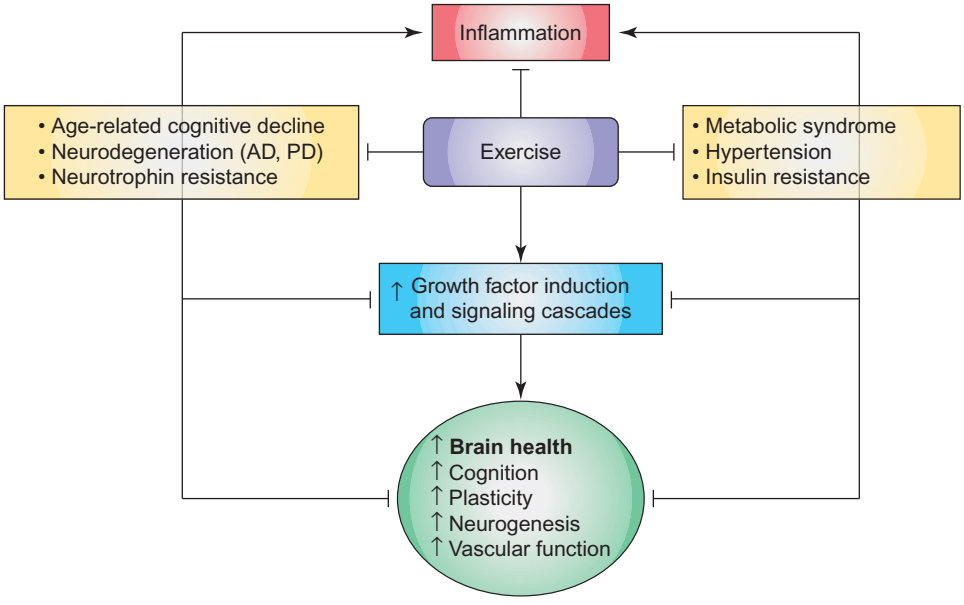

FIGURE 16.52 Physical exercise builds brain growth factors. A ongoing balance exists between factors like stress and the constant rebuilding of the brain and body. Exercise induces growth factors, helping to maintain cognitive functions, synaptic plasticity, neurogenesis, and vascular function. Exercise also reduces hypertension and insulin resistance. Chronic inflammation also is reduced by moderate exercise. It has been shown to reduce and delay the risk of neurodegenerative disorders like Alzheimer's and Parkinson's disease. *Source*: Cotman, Berchtold and Christie, 2007.

aging. And in nerve cells, genes also control moment-to-moment events like learning and falling asleep.

The environment and genes interact in all stages of brain development, including proliferation, differentiation and migration, axonal guidance, and synapse formation. Gene expression in human brain cells can be changed, within limits, by selectively turning stretches of DNA on or off. Such 'epigenetic' flow

of control runs 'on top of' (epi-) the flow of normal top-down causation. Epigenetics has now become crucial to the study of learning.

Messenger molecules in the brain are of two kinds: transmitters and modulators. We can define *neurotransmitters* as having very *local* effects in the synapse between two neurons, although there might be billions of such neurons and synapses. To date, more than 100 neurotransmitters have been identified. These brain chemicals are closely regulated: if the synapse has too little of a neurotransmitter, its message will not be sent. On the other hand, too much of the signaling molecule is generally toxic, and can kill nerve cells. For that reason there are pervasive *negative feedback loops* in any chemical pathway, much like tiny thermostats that keep the quantity of any molecule within safe limits.

Glutamate and *GABA* are the two most common neurotransmitters in the brain. Ninety percent of the neurons in cortex use glutamate, the primary *excitatory* neurotransmitter, which *increases* the probability of the next neuron firing when a precise number of molecules are released into the synapse. Too much glutamate is toxic and is specifically called *excitotoxic*. Excitotoxicity due to excess glutamate is one of the most harmful aspects of brain damage and disease. That is why it is essential to keep the levels of glutamate as low as possible, without interfering with the transmission of excitatory signals.

Glutamate can evoke two molecular receptor cascades, one involving NMDA and the other AMPA. Both of those substances are vital in the process of learning. NMDA increases the membrane voltage, while AMPA decreases it. The balance of NMDA and AMPA determines what kind of learning will take place at the target membrane of the glutamate synapse. NMDA is associated with long-term potentiation (LTP), making the synapse more excitable over time. AMPA is associated with long-term depression (LTD), which makes it less excitable. The first LTP system to be studied in detail was the glutamate synapse, by far the most common excitatory synapse in the brain. LTP and LTD require protein synthesis to grow the number of synapses, add synaptic spines, and increase the flow of neurochemicals (typically proteins) to all parts of the system.

The brain is the most energy-intensive organ in the body. The brain therefore generates a large concentration of free radicals and potential inflammatory events. Chronic inflammation is a major factor in degenerative diseases, including neurodegenerative disorders like Parkinson's and Alzheimer's diseases. Regulation of chronic inflammation is essential for maintaining a healthy nervous system. The synapse and the extracellular space are two locations that are vulnerable to a loss of chemical control because they are not embedded in the self-regulation machinery of the cell. Cleaning up the synapse is a good illustration of the general need to control the buildup of toxic molecules. The nervous system has evolved a number of ways to keep the concentration of potentially harmful molecules in the synapse under precise control. The three general types of synaptic 'clean-up' are *diffusio*, *degradation*, and *recycling* of the neurotransmitter.

We stated above that neurotransmitters have very local effects in the synapse between two neurons. *Neuromodulators*, on the other hand, are produced by quite small clumps of cell bodies below the cortex, and are spread very widely. These cells – typically just a few thousand – project their branches through sizable parts of the brain. Where they terminate, they 'spray' their messenger molecules. Thus neuromodulators can change large regions of the brain, whereas neurotransmitters act locally in nano-level synapses. Neuromodulation from small nuclei in the basal brain shapes the general activity of the cortex and basal ganglia.

Remember that the same molecule may play two different roles, depending on where it is secreted. Acetylcholine and glutamate can either be neurotransmitters or neuromodulators. As neuromodulators they modify large swathes of brain territory by regulating local synaptic signaling among billions of neurons and synapses. For example, neuromodulators may change the baseline membrane voltage of a population of cells, and thereby modify their local synaptic signaling. By switching neuromodulators between waking, sleep, and REM dreaming, the brain can control the balance between sensory inputs versus internal processes, for example. In waking, sensory signals flow freely, but they may be blocked or turned down during slow-wave sleep and REM. The difference is controlled by the widespread neuromodulation of those states.

The body is constantly maintained by molecules – called growth factors – such as human growth hormone. Two growth factors are also important in learning: neurotrophin and BDNF (for brain-derived neurotrophic factor). Neurotrophin is driven by the firing rate of neurons, and by the flow of neurotransmitters across the synapse. Physical exercise builds brain growth factors. An ongoing balance exists between factors like stress and the constant rebuilding of the brain and body. Exercise induces growth factors, helping to maintain cognitive functions, synaptic plasticity, neurogenesis, and vascular function. Exercise also

reduces hypertension and insulin resistance. Chronic inflammation is also reduced by moderate exercise.

In this chapter, we explored the molecules of cognition that help to carry brain signals and perform the computations that make the human mind possible. While it is a complex topic, understanding it will enable us to elucidate the fundamental processes that underlie our mind-brain!

9.0 CHAPTER REVIEW

1. Name five molecules that are highly conserved. What were their previous functions? What are their brain functions?
2. DNA operates over several time scales. What are they?
3. How do Hox genes affect brains? How is the developmental schedule of the brain affected by genes? What is the role of FOXP2?
4. What is the Central Dogma of molecular biology? How has it been changed by recent developments? Define 'epigenetic' and give an example.
5. Brain signaling molecules are of two kinds. What are they? How do their actions differ?
6. What is the most common neurochemical in the cortex? The second most common one? What different roles do they play?
7. How can the same signaling molecule have different receptors? What is a well-known example?
8. How can normal neurotransmission lead to brain dysfunction?
9. What two kinds of 'learning effects' are believed to exist at the synaptic level? What levels of the molecular machinery of the cell are believed to be involved in each of them?
10. What two types of cells are involved in information processing in the brain?

CHAPTER APPENDIX

TABLE 16.3 Other neurotransmitters

Chemical class	Example	Cell of origin	Storage	Release and other mechanisms of initiating signaling	Inactivation	Receptors
Acetylcholine	Acetylcholine	Neurons	Vesicles	Depolarization	Enzymatic (acetylcholinesterase)	Ionotropic (nicotinic) and GPCR (muscarinic)
Arnino acids	Glutamate	Neurons	Vesicles	Depolarization	Transporters	Ionotropic and GPCR
Monoamines	Dopamine	Neurons	Vesicles	Depolarization	Transporter	GPCRs
Peptides	Enkephalin	Neurons	Vesicles, often separate from small molecule neurotransmitters	Repetitive depolarization	Enzymatic (for many peptides relevant enzymes or other mechanisms are unknown)	GPCRs μ, δ, opiate receptors
D-Amino acids	D-Serine	Astrocytes (glia)	Unknown	Activation of serine racemase followed by release of resulting d-serine by unknown mechanisms	Transporter	Modulatory (glycine) site on NMDA glutamate receptors
Purines	Adenosine	Neurons and probably others	ATP is stored in vesicles and may be rapidly hydrolyzed to adenosine after release; high basal extracellular levels represent unstored adenosine	(1) Liberation from diverse extracellular purines by ectoenzymes (2) Facilitated diffusion out of cells	Transporter	GPCRs
Gases	NO	Neurons	None	$Ca2^{+}$-dependent regulation of nitric oxide synthase (nNos) to produce NO for immediate diffusion	Diffusion. Perhaps enzymatic degradation	Many enzymes containing transition metals; such as soluble guanylyl cyclase
Lipids	Anadamide	Neurons	Unknown if stored	Probably released info synapse but diffusion mechanism in aqueous medium unclear	Transporter followed by hydrolysis	GPCRs (cannabinoid)

(1) These examples are not fully extendible to the class. For example, the purine adenosine triphosphate (ATP), which despite its ubiquity as an energy carrying molecule can also carry information [10], is colocalized in vesicles with other neurotransmitters, such as acetylcholine or dopamine, and is released by depolarization; while the purine adenosine is released by facilitated diffusion. ATP interacts with both ionotropic receptors (P2X receptors) and G-coupled receptors (P2Y receptors), while adenosine only interacts with G-coupled receptors.
(2) As alluded to in the text, glia may, in some cases, be directly involved in neurotransmitter action: for example, by inactivation of neurotransmitter, such as glutamate, or by release, for example, of ATP or d-serine [11].

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Appendix

Methods for observing the living brain

Thomas Ramsøy, Daniela Balslev, and Olaf Paulson

OUTLINE

1.0 HISTORICAL BACKGROUND

1.1 Correlating brain and mind

Understanding the complex functions of the brain, including sensation, motor function, consciousness, and thoughts, has always triggered our curiosity. The brain is activated when we are engaged in solving a task, such as thinking, speaking, or purposeful movements. The activation is accompanied by local changes in the cerebral blood flow in the activated, i.e. involved, brain regions and this forms the basis for functional brain mapping studies. In the following, we provide a brief overview of some of the milestones in this field.

It was recognized early that a hemispheric lesion led to contralateral palsy, a loss of the ability to move a body part. If the lesion was on the left side, language disturbances could occur. In the 19th and the beginning of the 20th century, the functional organization of the brain was investigated through clinical-pathological correlations. Detailed descriptions of symptoms were subsequently (after the patient's death) related to autopsy findings, enabling the localization of specific functions in the brain. The main limitation of this method is that human brain lesions are accidental and thus unspecific in terms of localization because the damage is diffuse and often extends to regions without relevance for the neurological deficit in question. Moreover, adaptive brain responses may modify the neurological deficits over time. With the clinical-pathological correlation we learn about deficits that occur if a given brain region is injured, i.e. for which functions a given brain region is essential. For example, it was lesion studies that taught us that Wernicke's and Broca's areas are both essential for normal language function.

These limitations have provided the incentive for parallel development of other methods that allow a

Cognition, Brain, and Consciousness, edited by B. J. Baars and N. M. Gage
ISBN: 978-0-12-375070-9

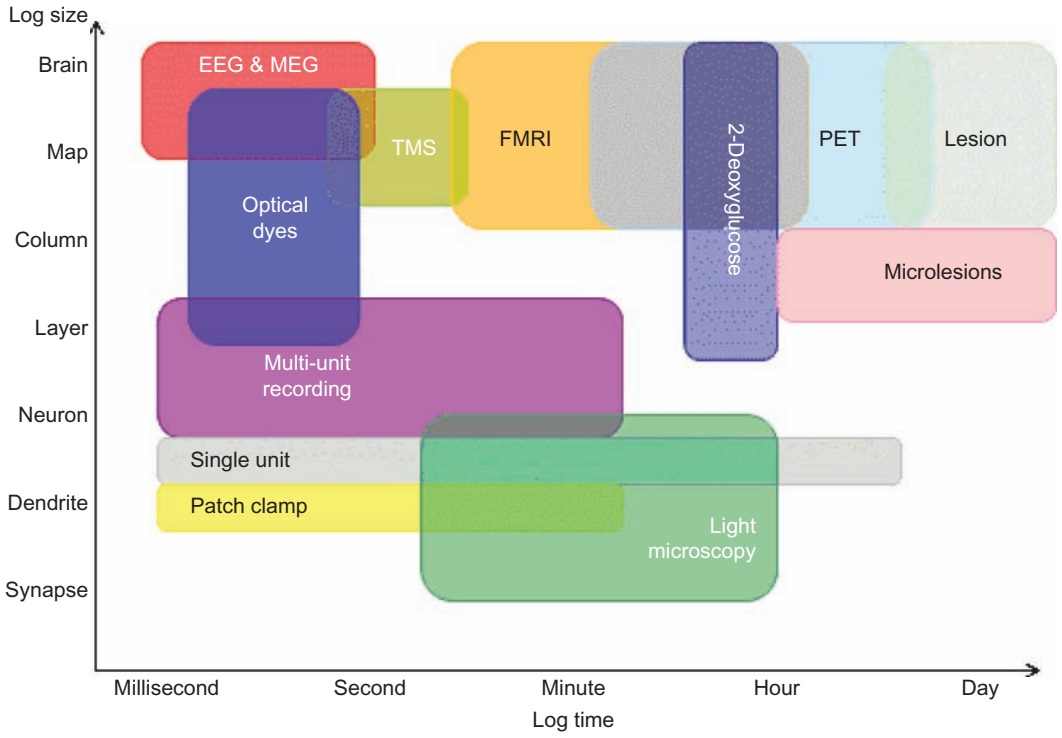


FIGURE A.1 Pros and cons of imaging techniques. Different imaging modalities have different resolution. While some approaches have a very high temporal resolution but a low spatial resolution, other modalities have an opposite relation. *Source*: Thomas Ramsøy, Daniela Balsler, and Olaf Paulson, with permission.

systematic study of the relation between brain and behavior in humans. The new neuroimaging techniques introduced toward the end of the 20th century measure changes in brain activity that correlate with a change in behavior. Current neuroimaging equipment can measure the changes in activity of brain volumes smaller than 1 mm^3 and as fast as tens of milliseconds (Figure A.1). The popularity of these new imaging methods is illustrated by the continuous increase in the percentage of studies that use them. For example, in 2005 every fifth published brain study was indexed by PubMed under the keywords PET (positron emission tomography) or MRI (magnetic resonance imaging) (Figure A.2).

The clinical-pathological correlation and the newer brain imaging methods both tell us about the functional organization of the brain, but fundamental differences separate these methods. Thus, with the clinical-pathological correlation, we learn what deficits occur if a given brain region is *injured*, i.e. for which functions a given brain region is essential. On the contrary, with PET and fMRI (functional MRI) we observe which regions are *activated* in a given task as compared with a control condition. Thus, from the clinical-pathological correlation, we know that Wernicke's and Broca's areas

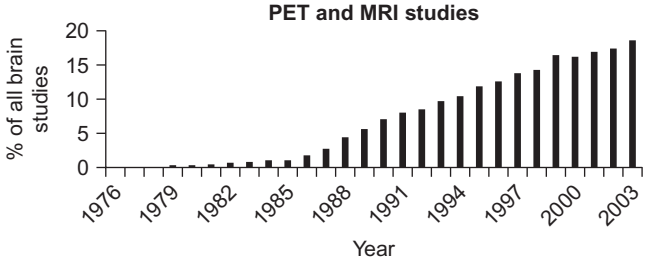


FIGURE A.2 The dramatic increase of neuroimaging in brain science. In 2005, every fifth published brain study was indexed by PubMed under the keywords PET or MRI. *Source*: Thomas Ramsøy, Daniela Balsler, and Olaf Paulson, with permission.

are essential for normal language function, but in any speech task, however, both sensory and motor areas involved in articulation will also be activated. For these reasons, sophisticated design of paradigms becomes essential in modern brain mapping. The task and control condition should, in principle, be identical except for the single psychological function whose location we want to map. It is practically very difficult, if not impossible, to control perfectly all behavioral parameters. For instance, in a paradigm designed to identify the neural correlate of spatial attention by presenting visual stimuli at either a cued or an un-cued location,

a change in activity in a brain area may as well reflect involuntary eye movements or the subject's effort to prevent a saccade towards the stimulus.

1.2 Recording brain activation

The brain is activated when we are engaged in solving a task, thinking, speaking, purposefully moving, etc. Such activation is accompanied by changes in the hemodynamics in the activated brain regions. This forms the basis for several functional brain mapping studies including the now dominating fMRI methods. In the following, a brief overview of some of the milestones in this field will be given.

Changes in hemodynamics during sensory, motor, and cognitive processes were observed about 130 years ago by Mosso in Italy (Mosso, 1881). He had a patient with a skull defect that allowed him to make external recordings of the 'brain pulse'. He saw changes in the brain pulse not only when the church bells were ringing but also when the man said a prayer even if he did it silently without words. About 10 years later, Roy and Sherrington (1890) proposed that there was a relation between the brain's function and its perfusion (blood flow). This theory has indeed been shown to be valid and has formed the basis for extensive research.

In the late 1920s Fulton (1928) observed a patient with an *intracranial arteriovenous malformation*, a condition where lesions of the cerebral vasculature develop such that blood flows directly from the arterial system to the venous system without passing through a capillary system. The patient complained of an abnormal sound (bruit) in the head, which was louder during reading. The bruit and its aggravation could be recorded, demonstrating that some kind of cerebral hemodynamic changes had to occur during reading (at least in this patient). In the late 1950s, it was demonstrated that stimulation of the brainstem resulted in activation in the EEG (electroencephalograph) as well as in cerebral blood flow increase (Ingvar and Söderberg, 1956, 1958).

In the mid-1960s, Cooper (Cooper *et al*., 1966) observed an increase of the oxygen tension locally in the brain during activation in patients undergoing surgery. This study further strengthened the fact that hemodynamic changes had to occur during cerebral activation. Moreover, this was the first study illustrating a change in the coupling between flow and metabolism during activation.

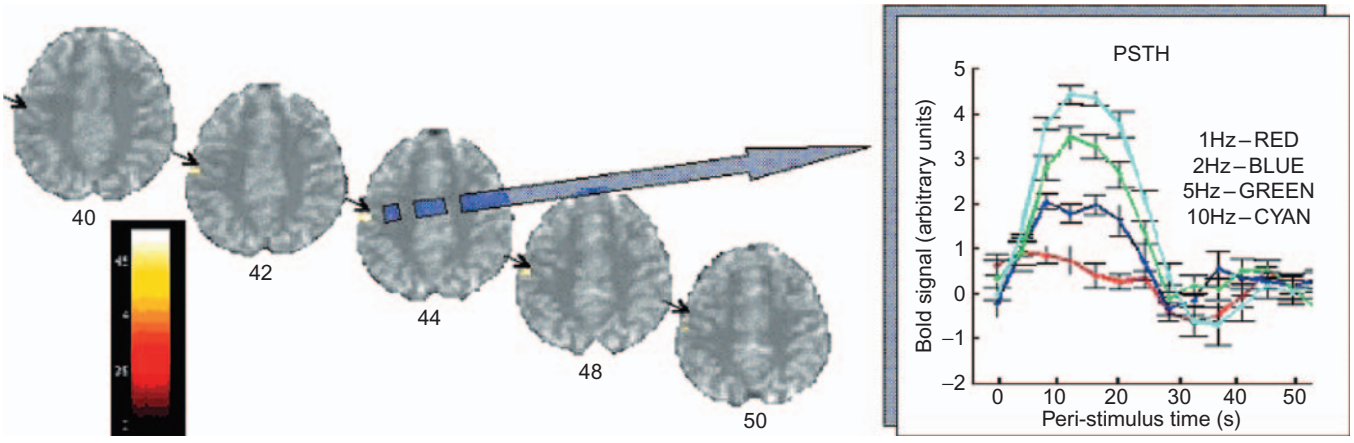
A milestone in investigation of regional cerebral function was achieved in the early 1960s when Lassen and Ingvar introduced the intra-arterial injection method using radiolabeled inert gases. In their first studies, they measured the clearance of the beta-imaging isotope ^{85}crypton from the exposed surface of the brain in experimental animals (Lassen and Ingvar, 1961). Soon the method was adapted for investigation in humans using the gamma-emitting isotope ^{133}xenon, which could be detected through the intact skull. Using multiple external scintillation detectors (sensors measuring ionizing radiation), it became possible to measure blood flow from as many as 250 regions. The method was used in the 1970s abundantly for functional localization in the brain and was, indeed, the first method used for functional brain mapping (Lassen *et al*., 1978). One drawback of this method was that the tracer had to be injected directly into the internal carotid artery, limiting studies to patients who were undergoing angiograms for diagnostic purposes.

In the 1970s, Sokoloff (Sokoloff *et al*., 1977) introduced the ^{14}C-deoxyglucose method for measurement of the metabolism of glucose in regions of experimental animals' brains. Soon the method was further developed for PET studies in humans with fluorinated deoxyglucose (FDG) labeled with the positron emitter ^{18}F. It is known that changes in blood flow and in glucose metabolism are coupled. Although measurement of a regional cerebral glucose metabolism in many aspects represents a milestone, it has not turned out to be very useful for measurement of the functional cerebral activation due to the limited time resolution (15–45 minutes) as compared to flow measurement with PET and fMRI to be discussed later in this chapter.

The establishment of PET in the 1980s and of fMRI in the 1990s provided new non-invasive methods suitable for studies of regional changes in the brain's hemodynamics as an expression of changes in regional cerebral activity. The non-traumatic nature of these methods has allowed investigation of not only patients but also normal subjects and thereby expanded research in functional cerebral activation.

2.0 METHODS

PET and fMRI are today the dominant methods for investigation of functional cerebral activation. Single photon emission computer tomography (SPECT) has features similar to PET, but has a lower resolution and is therefore less suitable for studies of functional activation. Other methods use the electrical and magnetic signal from the working brain produced by the activity in the neurons. These methods are



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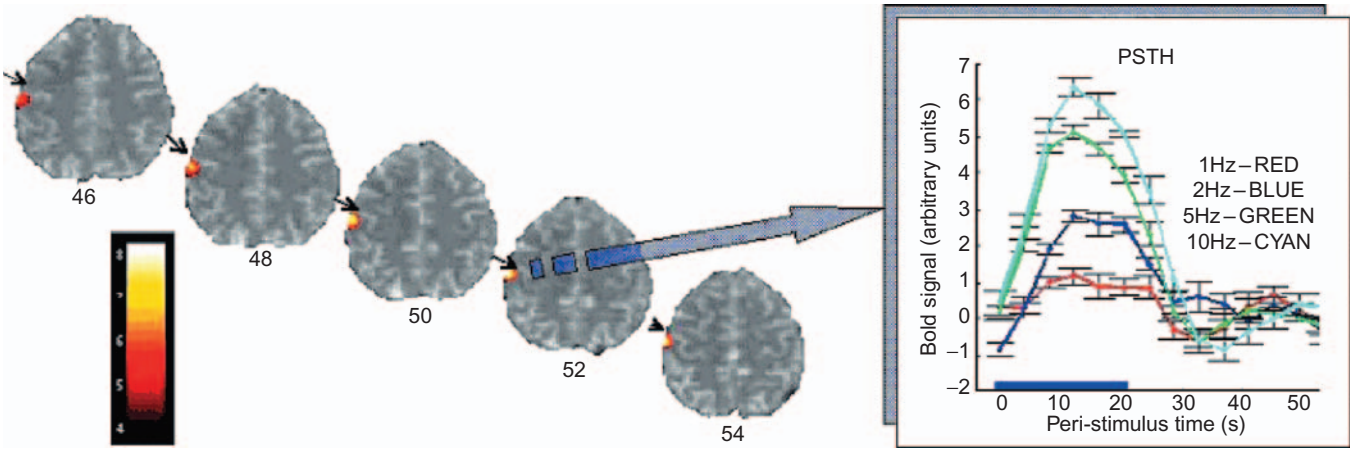

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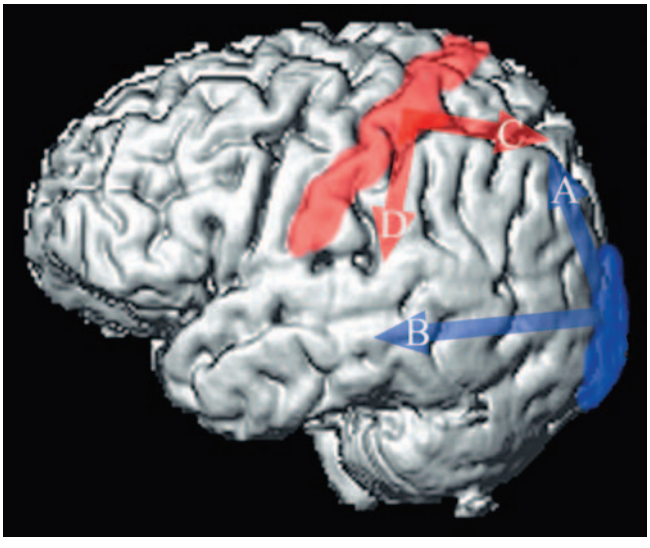


FIGURE A.3 The BOLD signal to finger stimulation. When the right finger is stimulated with a mild electrical shock, the change in blood flow can be picked up on the left hemisphere in the somatosensory body map. This is the blood oxygen-level dependent or BOLD response of fMRI. (a): Averaging brain slices. (b): The blood oxygenated-level dependent signal change (hemodynamic response) after the neural activation. *Source*: McConigle in Frackowiak *et al.*, 2004.

electroencephalography (EEG) and magnetoencephalography (MEG) and feature an excellent time resolution of about 10 milliseconds at the cost of limited localizing ability. Research using EEG has gained new interest when combined with fMRI, because it takes advantage of both the spatial resolution of fMRI and the temporal resolution of EEG. MEG is a research field which is currently expanding.

All these methods manipulate behavior and measure a change in brain activity. A complementary category of methods, including lesion studies or transcranial magnetic stimulation (TMS), allows manipulation of the brain in order to measure the effect on behavior. TMS induces an electric current in the brain whose effect is either stimulatory or inhibitory for the neuronal activity, depending on the parameters of the current induced. Using such a 'virtual lesion' mode, this method can reduce the excitability of a brain area with effects that mimic a brain lesion. TMS is a promising tool for confirming brain-behavior links identified with functional imaging. If an activated brain area is indeed essential for task performance, then its inactivation should change the subject's behavior during the task.

2.1 Electroencephalography (EEG)

Electroencephalography is a neurophysiological measurement of electrical activity in the brain. This recording is performed by placing electrodes either on the scalp or directly on the cortex. The resulting brainwave output is referred to as an *electroencephalogram* (EEG), originally named by the German psychiatrist Hans Berger (Berger and Gloor, 1969). Work on EEG techniques had already been performed by Richard Caton (Caton, 1875) and Vladimir Vladimirovich Pravdich-Neminsky (Pravdich-Neminsky, 1913). EEG is today used in clinical settings to assess brain damage, epilepsy, and other brain disorders. In many jurisdictions around the world it is used to assess brain death. It is also a cognitive neuroscience research tool due to its superior temporal resolution and its results are often compared to other brain recording techniques.

The EEG ranges from several to about 75 μV in the awake and healthy individual. The EEG signal as such is mostly attributable to graded postsynaptic potentials occurring in the cell body and large dendrites. The pyramidal cells of layers 3 to 5 are the major contributing units to the signal and these neurons are synchronized by rhythmic discharges from thalamic nuclei. The degree of synchronization of the underlying cortical activity is reflected in the amplitude of the EEG. Not surprisingly, most of the signal recorded in the EEG stems from the outer cortical layers near the electrode and the folded organization of the cortex in humans contributes to the electrical summation of neuronal signals rather than mutual cancellation.

The EEG recorded at the scalp represents a passive conduction of currents produced by summating activity over large neuronal aggregates. Regional desynchronization of the EEG reflects increased mutual interaction of a subset of the population engaging in 'cooperative activity' and is associated with decreases in amplitude. Thus, from the raw EEG alone it is possible – even for the untrained eye – to determine the level of synchrony. To the trained eye, it is also possible to see pathological patterns following states such as epilepsy. As can be seen in Figure A.4, it is possible to make out some basic differences in healthy and pathological brain activation.

In general, we can think of the EEG as two kinds of measures. First, *spontaneous activity* is the activity that goes on continuously in the living individual, as measured on the scalp or directly on the cortex. The measurement of this signal is what we call the encephalogram, which can be thought of as a measurement of electrical signals within a time window, but with no additional time factors. The amplitude of the EEG is about 100 μV when measured on the scalp and about 1–2 mV when measured on the surface of the brain (intracranial recording). The bandwidth of this signal is from under 1 Hz to about 50 Hz. Figure A.4 displays different kinds of spontaneous EEG activity. Today, the EEG is used extensively for clinical purposes, especially in testing for epilepsy, but recently, the combination with imaging methods with high spatial resolution, such as fMRI, has led to renewed interest in the EEG.

The second kind of EEG measure, *evoked potentials* (EP) and *event-related potentials* (ERP), are components of the EEG that arise in response to a stimulus (e.g. auditory, somatosensory, or visual input). Such signals are usually below the noise level and not normally possible to distinguish in the raw EEG output. In order to see the effects of the stimulus, one must apply a train of similar stimuli and then average the signal for all these epochs. In this way, the signals recorded at the time of a stimulus are grouped into one category. Averaging the signal for a time frame cancels out any spontaneous fluctuation in the EEG and it is therefore possible to make out and display the signal intensity within a time frame common to all stimulus epochs. So, for a visual stimulus, such as a word, we get different waves of increase and decrease in signal intensity (Figure A.5). Each of these components is today identified as a relevant indicator of cognitive processing states. For example, EEG recordings of a subject reading a word show early increases or decreases indicative of early visual processing and the drawing of attention to the stimulus and later we find a significant peak after approximately 400 milliseconds thought to indicate semantic processing. This component is called the P400, where P = a positive signal change.

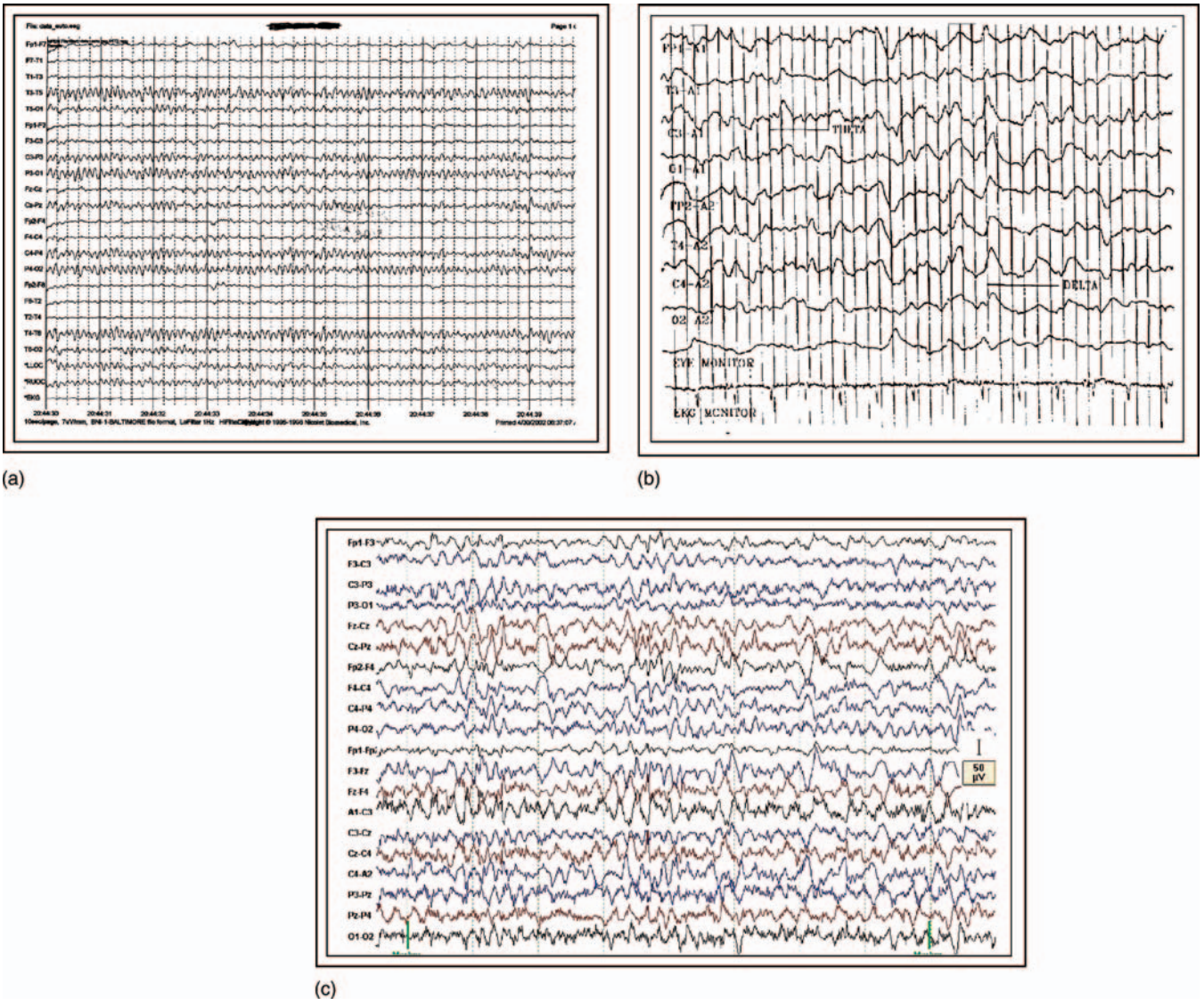


FIGURE A.4 The raw EEG in different states. (a) The record of a healthy and awake individual shows different low-amplitude and high-frequency bands of activation, indicative of rapid communication between ensembles of neurons. (b) When going to sleep the brain can operate at several different levels of sleep, ranging from rapid eye movement (REM) sleep to stages of deep sleep. Deep sleep stages display high-amplitude and low-frequency patterns, which indicate lower cooperation between and within brain areas. (c) Finally, epileptic seizures show up clearly on the EEG as both high-amplitude and relatively high-frequency patterns on all recorded channels. This demonstrates that most parts of brain are affected by the seizure. This pattern of activity is indicative of areas that get into a mutual loop of activation, eventually leading to chaos and non-information processing in the brain. *Source*: Thomas Ramsøy, Daniela Balsler, and Olaf Paulson, with permission.

An example of a well-known component using ERP is called mismatch negativity (MMN), sometimes also called the mismatch field. Consider that you are listening for a stream of similar beep sounds, and suddenly the sound changes. The brain responses to this deviant sound, based on differences in pitch, duration, or loudness, can be elicited regardless of whether the subject is paying attention to the sequence.

At the ERP curve, this event occurs with sources in the primary and nonprimary auditory cortex and a typical latency of 150–250 ms after the onset of the deviant stimulus. Although the exact nature of the MMN is not well understood, it is thought to reflect an automatic and early response to violation of an automatically formed, short-term neural model or memory trace of physical or abstract environmental regularities (Näätänen and Winkler, 1999; Näätänen, Paavilainen, Rinne, and Alho, 2007). Alternatively, it is possible that the MMN reflects changes in neural ensembles, and that the response of newly recruited networks, compared

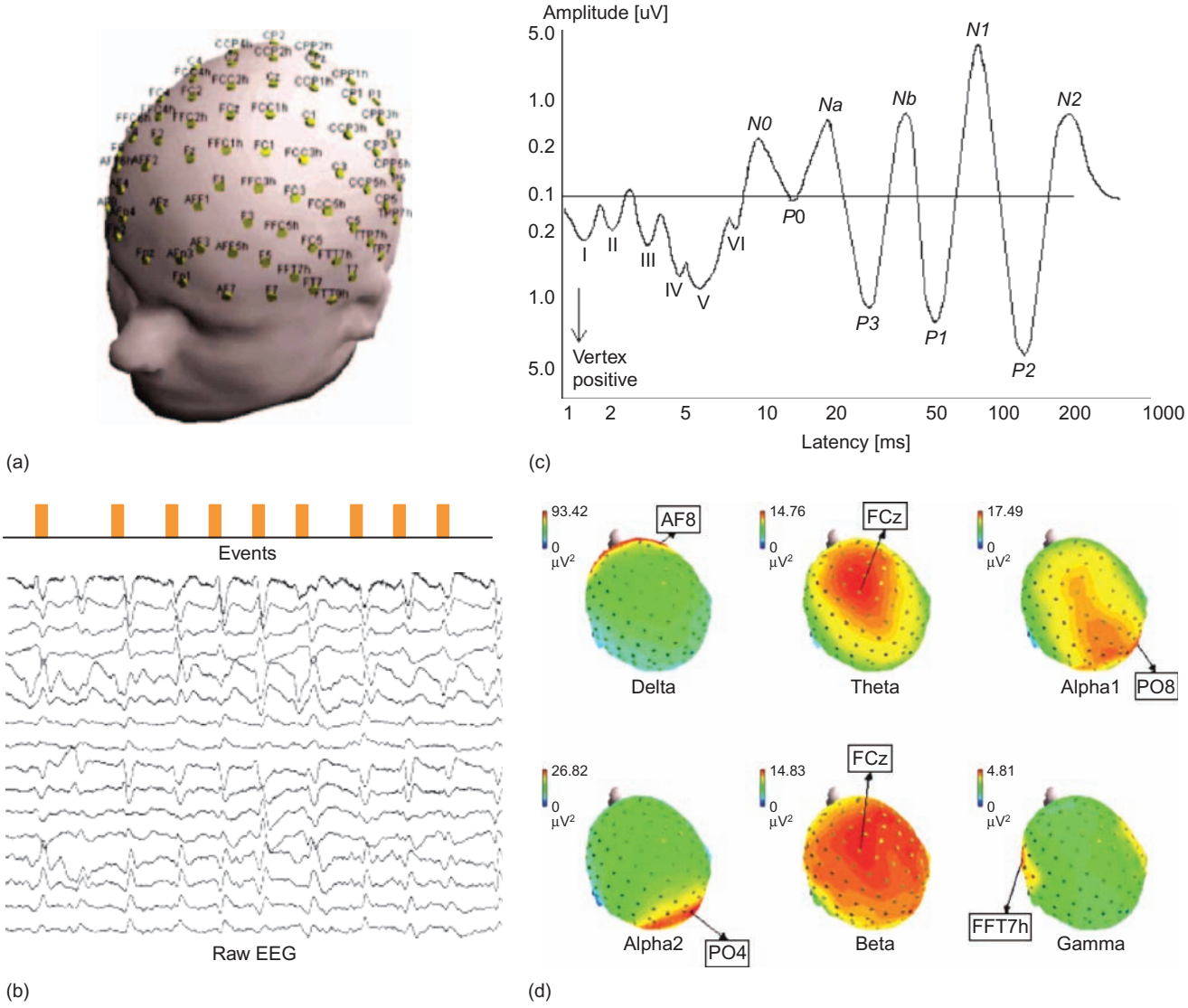


FIGURE A.5 The raw electroencephalogram and two ways to analyze it. (a) A number of electrodes are placed on specific places around the scalp according to a prespecified system. (b) The readouts from each of these electrodes, or channels, can be plotted as separate curves over time and make up the raw encephalogram. Events such as sound stimuli can be plotted on the same time curve, both to give an idea of trends in the raw EEG, but also to be used in the later averaging of the data. The events are shown for illustrative purposes. (c) The event-related analysis of the raw EEG is made by averaging the EEG signal changes at the time interval around each stimulus event. By averaging the signal spontaneous activation is cancelled out, while the signal change common to all stimulus events will be visible. In this way, several components have been determined. These include early positive or negative peaks thought to involve subcortical activations (e.g. from the brainstem) and later onsets thought to involve more elaborate, cognitive processes. An example is the P400 component (P400 = positive peak around 400 milliseconds after stimulus onset, not shown here), which is thought to be an indicator of semantic processing. Finally, more recent developments have made it possible to analyze the data both in terms of the EEG bandwidths during a period and the relative spatial localization of these. (d) The EEG power spectrum topography shows the average bandwidths at rest. As can be seen, delta activity is focal at the prefrontal site and maximal at the AF8 electrode site. Theta activity is found at the frontal midline area, maximal at the FCz electrode site. Alpha-1 activity was centered on the parietal-occipital midline area and maximal at the PO8 electrode site. Alpha-2 activity was focal at the occipital area and maximal at the PO4 electrode site. Beta activity was highly diffused across the scalp and a maximal site at the FCz electrode site was selected. Gamma activity was focal at bilateral temporal areas and maximal at the FFT7h electrode site. *Source*: (a) and (d) Andrew *et al.*, 2006; (b) and (c) chapter authors, with permission.

BOX A.1 The electromagnetism of meditation

A very interesting study by Lutz *et al*. (2004), using EEG, focused on the brain activity of experienced Buddhist meditators. In this study, EEG signals were recorded in expert meditators and meditation-naïve control subjects during normal resting phases and during different stages of meditation. Three task stages were used: baseline rest, meditative state, and a pause stage between meditative states. Lutz *et al*. found that, during meditation, the group of experienced meditators had a dramatically higher level of gamma-band oscillations. The researchers also found a long-distance phase synchrony between frontal and parietal areas in the brain. From these results, Lutz *et al*. speculate that meditative training enhances the integration of distant brain areas. Interestingly, the results also showed that the brain activation even at rest before meditation practice differed between the expert and naïve groups. This indicates that substantial meditative experience can alter the workings of the brain, although at present we can only speculate at the precise cause and effect relationships.

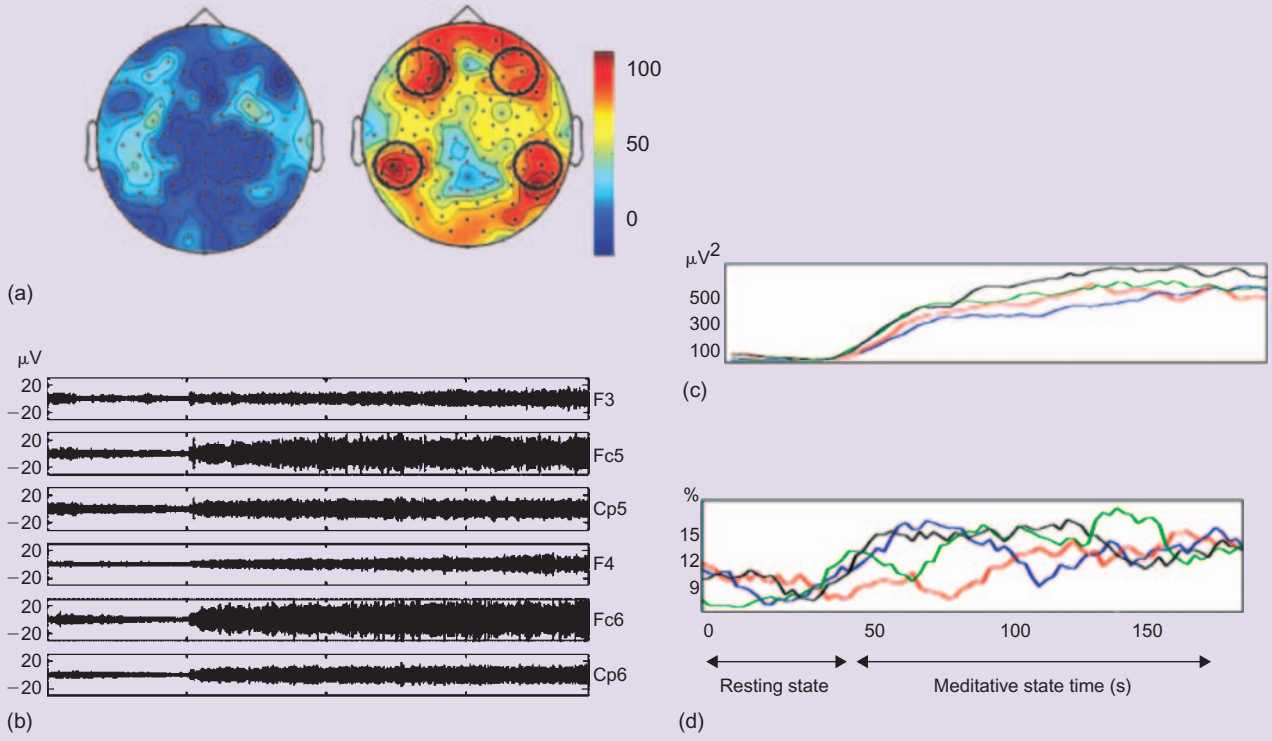


FIGURE A.6 Measuring the brain effects of meditation: the study of Lutz *et al*. (2004) shows that the absolute gamma power during mental training is much higher in practicing meditators (right) as compared to non-meditating controls (left). The color scale indicates the percentage of subjects in each group that had an increase of gamma activity during the mental training. *Source*: Lutz *et al*., 2004.

to networks that have processed the repeated stimulus, respond more vigorously (Näätänen, 1992; Jääskeläinen *et al*., 2004).

The ERP shows how it is possible to identify specific activation patterns within the brain according to the changes in signal intensities across time. Although EEG is traditionally thought of as superior in temporal resolution but with poor spatial resolution, continuous technical developments have improved the spatial resolution dramatically. Today, EEG is performed by applying hundreds of electrodes on the scalp, typically by using a head cap with predefined positions. As a research tool, EP/ERP can thus provide valuable information about both the precise timing and now also the gross cortical distribution of the activity generated during mental activity.

2.1.1 *Intracranial EEG and deep electrodes*

Not all EEG recordings are done from the outside of the skull. In some cases, it is also possible to record the electrical properties directly from the brain itself. There are, in general, two ways of doing this: by laying an intracranial grid of electrodes on the surface of a part of

the brain; or by using deep electrodes directly into the brain. Both methods are invasive and are only applied in humans as part of a clinical evaluation, typically in the search for epileptic foci for surgical planning. In this clinical procedure, the surgeons need to know not only where the epileptic seizure initiates, but also where other important cognitive functions are located. If possible, surgeons avoid ablating brain tissue that is involved in a cognitive function such as memory or language. Therefore, the patient needs to be awake during the test, both in order to respond to the set of cognitive tasks that are applied and, in order to report any changes occurring during the test. While the electrodes are implanted, researchers are sometimes allowed a limited time to do scientific testing on these patients.

In a study of intracranial deep electrodes in humans, Quiroga and colleagues (Quiroga *et al*., 2005) recorded the response of single neurons in the medial temporal lobe when subjects saw images of faces and objects. Remarkably, a subset of the neurons responded selectively to strikingly different pictures of specific famous people, landmarks, or objects. In other words, they found that one neuron responded specifically to pictures of actress Jennifer Aniston, another neuron responded significantly more to pictures of actress Halle Berry, and yet another neuron responded most to the Sydney Opera House (Figure A.7). This finding demonstrates an invariant, sparse, and explicit neural code that may be important in turning visual percepts into memories.

While deep electrodes are implanted in the brain, it is possible to reverse the electrical current and stimulate the same area of the brain. In this way, one may grossly activate a highly specific region of the brain. By using this method, Barbeau and colleagues (Barbeau *et al*., 2005) found a difference in the subjective reports of subjects when stimulating the hippocampus or the adjacent perirhinal cortex, both areas within the medial temporal lobe. When stimulating the hippocampus, their patient reported full-blown episodic memories in rich detail and with scenic and episodic content. When stimulating the perirhinal cortex (Figure A.8), the patient reported recollection of a specific object that later developed into a full-blown episodic memory. While this study is limited by only using a few experimental stimulations and therefore should be interpreted with caution, the results indicate that areas within the medial temporal lobe play different roles in memory and recall. It seems that the hippocampus is involved in the recall of full episodic memories, while the perirhinal cortex is more involved in specific object memory.

Intracranial imaging is also done on non-human primates such as the macaque monkey. This animal 'model' of the human cognitive system allows scientists to further their exploration of the neural correlates of cognitive functions. Important discoveries have been made using this approach, such as the findings of mirror neurons made by Gallese and colleagues (Gallese *et al*., 1996).

Together, EEG presents a whole range of different recording (and stimulation) approaches that each makes significant contribution to the study of brain-mind relationships. With its superior temporal resolution, the EEG provides valuable information to combine with other imaging techniques that have a high spatial resolution. We will return to the combination of such data at the end of this appendix.

2.2 Magnetoencephalography (MEG)

Magnetoencephalography (MEG) is the measurement of the magnetic fields produced by electrical activity in the brain, usually recorded from outside the skull. It is a highly interesting tool for investigation of functional activation of and connectivity in the brain. The spatial resolution with the most advanced instruments comes down to a few millimeters and the temporal resolution is, as with EEG, down to milliseconds. This allows us to record how activation spreads from one region to another.

2.2.1 The principles of MEG

The physical principles of MEG are based on the old observation from H. C. Ørsted from 1820 that an electrical current in a wire will generate a surrounding circular magnetic field. Since impulses propagating in the brain are generated by electrical currents, an abundant amount of small local magnetic fields will be generated. The magnetic field from a single neuron is far below detection level; however, the combined fields from a region of about 50 000 active neurons can give rise to a net magnetic field that is measurable.

Let us for simplicity consider a single electrical wire which will be surrounded by a circular magnetic field orthogonal to the electrical current. If it corresponds to an electrical current in the brain, an electrical dipole, parallel to the surface of the skull, then the magnetic field will exit the skull on one side of the current and re-enter the skull on the other side. Changes in the electrical current in the brain and in the magnetic field will

FIGURE A.7 Quiroga and colleagues (Quiroga *et al.*, 2005) found a neuron in the left posterior hippocampus that selectively responded to different views of the actress Jennifer Aniston. Responses in 30 of a total of 87 images are shown (*inset*: the responses to images of Jennifer Aniston). Numbers indicate the image number; graph indicates number of neural spikes recorded. Similar findings were made in other neurons for other stimuli, including the actress Halle Berry and the Sydney Opera House. *Source*: Quiroga *et al.*, 2005.

induce an electrical current in a circular lead placed parallel to the surface of the skull. The induced current will change direction if the lead is moved from one side to the other of the current in the brain (Figure A.9). If, by contrast, an electrical current in the brain is perpendicular to the surface of the skull, then no magnetic gradients are produced outside the skull and an external lead will remain silent.

The electromagnetic signals in the brain derive from the net effect of ionic currents in the dendrites

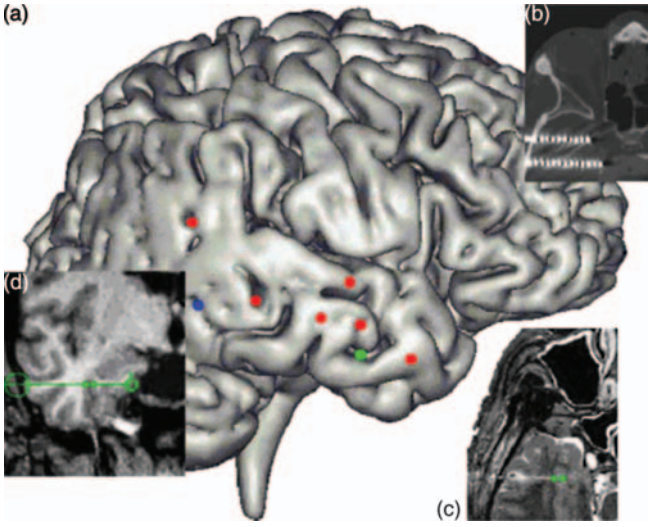
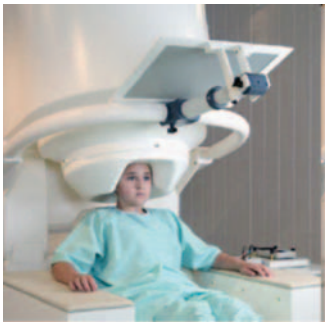
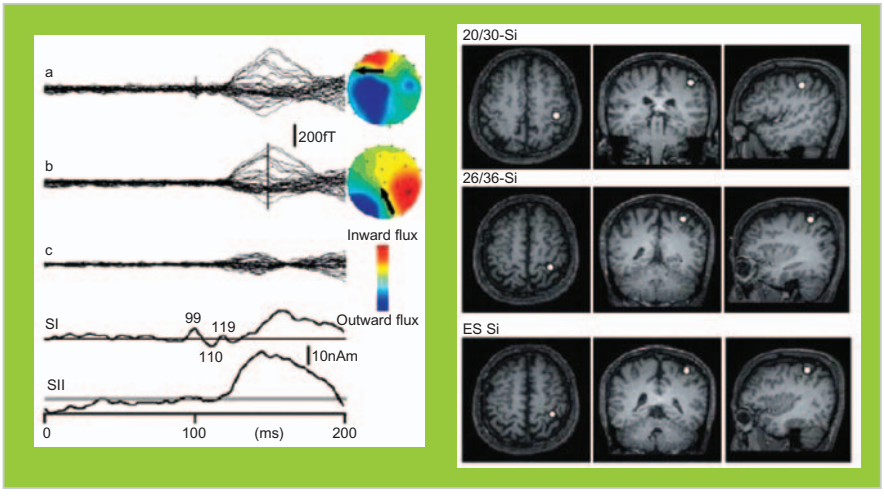


FIGURE A.8 The stimulation of perirhinal cortex in object memory. (a) Image reconstruction of the patient's brain with the site of implantation of each electrode. The green line shows the implantation site of the electrode running through the perirhinal region. Red and blue dots indicate other electrode implantation points in the same brain. (b) A CT scan showing contact location of the electrodes (white dotted lines). (c) Axial MRI structural scan showing the thin trace left by the electrode (white line). (d) Coronal MRI scan showing the stimulation site (green dots) in the depth of the occipitotemporal sulcus of the right temporal lobe, an area that corresponds to the perirhinal region (see text for discussion). *Source*: Barbeau *et al.*, 2005.





Magnetic field

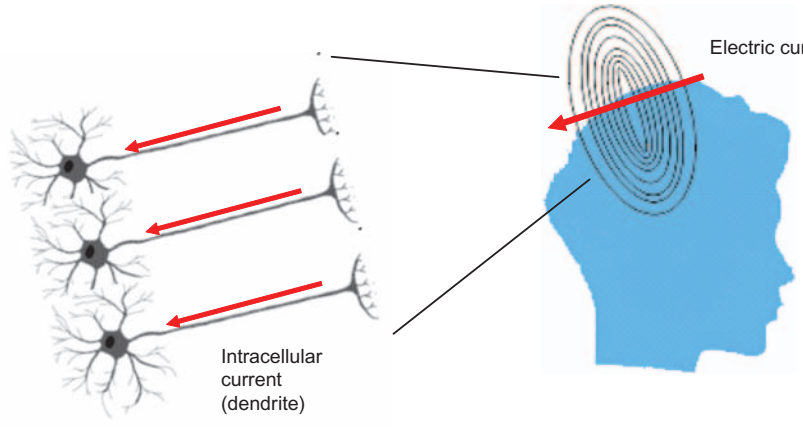


FIGURE A.9 Magnetoencephalography and its analyses. The subject is placed in the scanner that has a large set of shielded sensors. The signals themselves derive from the net effect of ionic currents flowing in the dendrites of neurons during synaptic transmission and in the extracellular medium as return currents (bottom). Action potentials do not produce an observable field because the currents associated with action potentials flow in opposite directions and the magnetic fields cancel out. *Inset left*: Magnetic fields following painful (epidermal) stimulation where (a) shows the recorded data; (b) and (c) display residual magnetic fields obtained after filtering the somatosensory processing signals from the recorded data. The bottom two lines show the time course of the source strengths during the painful stimulation. *Inset right*: Source locations of the MEG data overlaid on MR images. *Source*: 4D Neuroimaging, San Diego, with permission.

of neurons and in the extracellular space as return currents during impulse propagation and synaptic transmission. Action potentials do not produce significant fields as the currents associated with action potentials flow in opposite directions, canceling out the magnetic fields.

From the above considerations on the direction of the electrical dipoles and generated magnetic fields, it appears that it is the neurons located in the wall of the sulci of the cortex with orientations parallel to the surface of the head that project measurable portions of their magnetic fields outside of the head. Thus, neurons on the top and in the bottom of the sulci will have an orientation which yields magnetic fields with minimal gradients outside the skull and will not be recordable. Still, deviation of the radial direction of the convex source by only 10 to 20 degrees can be enough to give a detectable signal. Therefore, it seems likely that especially the convex sources near the skull and thus near the recording apparatus contribute significantly to the MEG signals.

2.2.2 MEG recording

The magnetic signal emitted from the working brain is extremely small, a few femto-Teslas (17 fT = 10^{-15} T[1]). Therefore, extremely sensitive and expensive devices such as the superconducting quantum interference device (SQUID) are used. The SQUID is an ultrasensitive detector of magnetic flux. It acts as a current-to-voltage converter that provides the system with sufficient sensitivity to detect neuromagnetic signals. In order to record these weak magnetic fields, shielding from external magnetic signals, including the Earth's magnetic field, is necessary. An appropriate magnetically shielded room can be constructed from mu-metal, which is effective at reducing high-frequency noise, while noise cancellation algorithms reduce low-frequency common mode signals. With proper shielding, the SQUID acts as a low-noise, high-gain current-to-voltage converter that provides the system with sufficient sensitivity to detect neuromagnetic signals of only a few femto-Teslas in magnitude.

The first detection of magnetic rhythm from the brain dates back nearly 40 years and used an induction coil magnetometer in a magnetically shielded room (Cohen, 1968). Modern systems have now up to about 300 SQUID channels placed around the head and have a noise level of around 5 to 7 femto-Teslas. This has to be compared to an overall magnetic field of the brain of around 100 to 1000 femto-Teslas.

2.2.3 Data analysis

The primary technical difficulty with MEG is that the problem of inferring changes in the brain from magnetic measurements outside the head (the 'inverse problem') does not, in general, have a unique solution. The problem of finding the best solution is itself the subject of intensive research today. Adequate solutions can be derived using models involving prior knowledge of brain activity and the characteristics of the head, as well as localization algorithms. It is believed by some researchers in the field that more complex but realistic source and head models increase the quality of a solution. However, this also increases the opportunity for local minima and potentially makes the numeric conditioning of the system worse, thus increasing the effects of model errors. Many experiments use simple models, reducing possible sources of error and decreasing the computation time to find a solution. Localization algorithms make use of the given source and head models to find a likely location for an underlying focal field generator. An alternative methodology involves performing an independent component analysis first, in order to sort out the individual sources, and then localizing the separated sources individually. This method has been shown to improve the signal-to-noise ratio of the data by correctly separating non-neuronal noise sources from neuronal sources, and has shown promise in segregating focal neuronal sources.

Generally, localization algorithms operate by successive refinement. The system is initialized with a first guess. Then a loop is entered, in which a forward model is used to generate the magnetic field that would result from the current guess and the guess is then adjusted to reduce the difference between this estimated field and the measured field. This process is repeated until a convergence between estimated and measured field is reached.

Another approach is to ignore the inverse problem and use an estimation algorithm to localize sources. One such approach is the second-order technique known as *synthetic aperture magnetometry* (SAM),

[1]The tesla is the value of the total magnetic flux (a magnet's 'power') divided by area. Hence, reducing the affected area will generally increase the magnetic flux density. The tesla is a unit to define the intensity (density) of a magnetic field. The Earth's magnetic field at latitude 50° is 5 μT (5.8×10^{-5} T) and on the equator at a latitude of 0° is 31 μT (3.1×10^{-5} T).

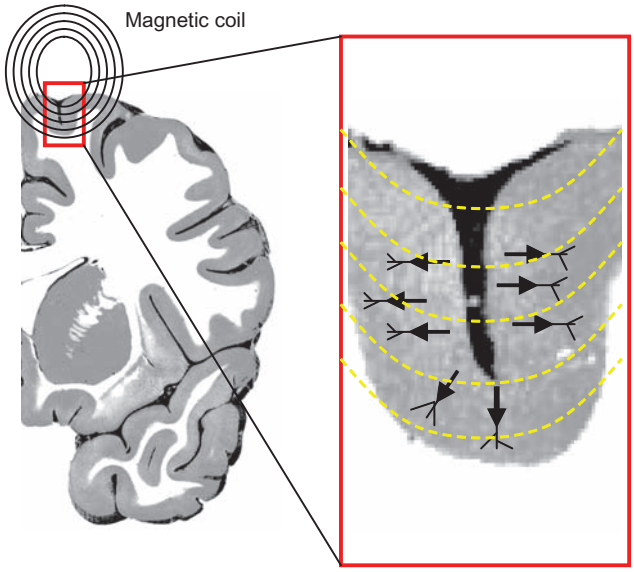


FIGURE A.10 The magnetic gradient of the neurons at the top and bottom of a sulcus do not have an orientation that maximizes their contribution to the MEG recording. The magnetic changes occurring in neurons on the sulci walls are better measurable by the MEG apparatus. *Source*: Adams *et al.*, 2004.

which uses a linear weighting of the sensor channels to focus the array on a given target location. This approach, also known as 'beamforming', has an advantage over more traditional source localization techniques because most sources in the brain are distributed and cannot be well described with a point source such as a current dipole.

A solution can then be combined with MRI images to create *magnetic source images* (MSI). The two sets of data are combined by measuring the location of a common set of fiducial points marked during MRI with lipid markers and marked during MEG with electrified coils of wire that give off magnetic fields. The locations of the fiducial points in each data set are then used to define a common coordinate system so that superimposing ('co-registering') the functional MEG data onto the structural MRI data is possible.

A criticism of the use of this technique in clinical practice is that it produces colored areas with definite boundaries superimposed upon an MRI scan: the untrained viewer may not realize that the colors do not represent a physiological certainty, because of the relatively low spatial resolution of MEG, but rather a probability cloud derived from statistical processes. However, when the magnetic source image corroborates other data, it can be of clinical utility.

2.2.4 Relation to other recording modalities

MEG has been in development since the 1970s but has been greatly aided by recent advances in computing algorithms and hardware and promises good spatial resolution and extremely high temporal resolution (better than 1 ms). Since MEG takes its measurements directly from the activity of the neurons themselves, its temporal resolution is comparable with that of intracranial electrodes. MEG's strengths complement those of other brain activity measurement techniques such as EEG, PET, and fMRI whose strengths, in turn, complement MEG. Other important strengths to note about MEG are that the biosignals it measures are not distorted by the skull, as in EEG (unless magnetic metal implants are present) and that it is completely non-invasive, as opposed to PET.

In research, the primary use of MEG is the measurement of time courses of activity as these courses cannot be measured using fMRI. Due to various technical and methodological difficulties in localization of sources using MEG, its use in creating functional maps of human cortex plays a secondary role, as verification of any proposed maps would require verification using other techniques before they would be widely accepted in the brain mapping community.

The clinical uses of MEG have until now essentially been limited to investigation of special cases for detecting and localizing seizure activity in patients with epilepsy and in localizing cortical pathology for surgical planning in patients with brain tumors or intractable epilepsy.

The physiological basis of the neuroimaging signal is the coupling between regional cerebral activation and blood flow and, further, the uncoupling between flow and oxygen consumption during activation. Put simply, an increase in activity in the cerebral tissue leads to a blood flow increase that can be measured with PET. The increase in flow markedly exceeds the increase in oxygen consumption so that the concentration of deoxyhemoglobin decreases. This local decrease in deoxyhemoglobin gives rise to the fMRI signal.

The epileptic seizure can be considered as an extreme non-physiological activation where all neurons fire at maximal rate. In this condition, blood flow is markedly increased and oxygen consumption is also increased but much less so, resulting in an increase in oxygen content in the cerebral venous blood (Brodersen *et al.*, 1973). This corresponds to the observation by Cooper and co-workers, described earlier, of an increased *oxygen tension* in cerebral tissue. Raichle and Fox, in an elegant PET study, demonstrated that

BOX A.2 Phantom limb sensation and brain plasticity

A good example of the application of MEG to study psychological or perceptual issues is a study done by Yang *et al*. (Yang *et al*., 1994) (see also Ramachandran and Hirstein 1998; Ramachandran and Rogers-Ramachandran 2000). These researchers studied the plastic changes that occur in the brain after amputation of a limb. Phantom limb sensations occur in almost all people who have a limb amputated. What this means is that people who lose their arm are still experiencing sensations from that arm, although it is not there! This phenomenon has been known throughout history – e.g. by Lord Nelson, whose phantom arm led him and others to think that the phantom was proof that the immaterial soul could exist without the physical body. Today, we are able to measure changes occurring in the brain of those unfortunate people.

It is possible to produce phantom limb sensations in these patients. For example, in an arm amputee, one may produce a phantom arm sensation by tickling the chin or jaw on the face on the same side as the amputation. By doing this, Yang *et al*. found that those areas that would normally be activated by stimuli to an intact arm now became activated by stimuli to either the face or the amputation stump on the patient. These findings demonstrate that amputation leads to a remapping of the primary somatosensory cortex and that one brain area can alter its functional connections, even in adults. Today, it is believed that amputation leads to three steps of change in the somatosensory cortex. First, amputation leads to a loss of input from the original sensory area. This then leads to functional changes in already existing connections within the somatosensory cortex. Finally, as these functional changes continue, they will eventually lead to changes in the physical connectivity between neurons.

Normally, adjacent areas that represent different body parts – e.g. face and hand areas – have tight interconnections. This facilitates the representations to be specific, in saying both 'this is input from the hand' and 'this is *not* input from the face'. When an arm is amputated (or even disabled for a prolonged time), it leads to such a remapping of the somatosensory cortex. This was clearly demonstrated by Yang *et al*.'s MEG study.

In the study by Yang and colleagues, stimulation of the face led to phantom sensations and was correlated to co-activation of both the face and hand representation areas in the somatosensory cortex. A nice feature in this study is that the non-affected hemisphere serves as a control condition. That is, in addition to looking at other, non-amputated, subjects, we can also compare the activation between the hemispheres. The study by Yang *et al*. is today considered to be among the very first studies to demonstrate plastic changes in the human brain.

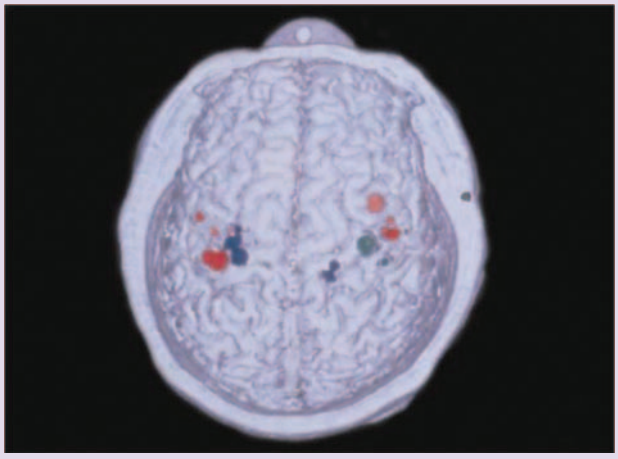


FIGURE A.11 Normally, adjacent areas that represent different body parts, for example, the face and hand areas, are tightly interconnected. This helps make the representations highly specific, in saying both, 'this is input from the hand' and 'this is *not* input from the face'. When an arm is amputated (or even disabled for a long time), it leads to such a remapping of the somatosensory cortex. This was clearly demonstrated by Yang *et al*.'s 1994 MEG study, where they reported that stimulation of the face led to phantom sensations in the missing (amputated) hand, which correlated to co-activation of both the face and hand representation areas in the somatosensory cortex. Clearly, a remapping had occurred in this patient. *Source*: Yang *et al*., 1994.

during normal physiological activation of the brain blood flow, as measured by $^{15}O_2$, and glucose phosphorylation, as measured by the ^{18}F-FDG, increase in parallel, whereas oxygen consumption only increases to a minor extent (Fox and Raichle, 1986; Fox *et al*., 1988).

Theoretical calculations suggest that a large share of the metabolic energy is spent on action potential propagation along axon collaterals (Attwell and Laughlin, 2001). However, empirical studies using simultaneous electrophysiological and hemodynamic recordings by Lauritzen and co-workers (Lauritzen, 2001) and by Logothetis and co-workers (Logothetis *et al*., 2001) have demonstrated that the increase in flow and BOLD (blood-oxygenation-level-dependent) signal reflects the increased synaptic activity and local field potentials in the dendrites, rather than a higher firing activity in the postsynaptic neurons. Thus, a release of stimulating as well as of inhibiting neurotransmitters will result in an increased metabolic turnover that increases blood flow and the BOLD signal.

2.3 Positron emission tomography (PET)

A modern PET scanner has more than 10 000 scintillation detectors registering the decay of positron emitting isotopes. When these isotopes decay, the emitted

positron will immediately meet a normal electron which merges and forms two gamma rays with energy of 511 keV[2] and an angle of precisely 180° relative to each other. When two detectors in the scanner register a photon of 511 keV exactly simultaneously, then a decay must have occurred on the line connecting these two detectors. At normal counting rates, the chance that two detectors simultaneously record two photons originating from two different positron decays is unlikely. Thus, it becomes possible to reconstruct a three-dimensional picture of the distribution of the isotope in the field of view of the PET camera.

The most used isotope compound for PET measurement of functional brain activation is $H_2{}^{15}O$. ^{15}O is a positron-emitting isotope with a half-life of only 2 minutes. For that reason, the isotope has to be produced in a cyclotron in the immediate vicinity of the PET camera. $H_2{}^{15}O$ is injected intravenously and will reach the brain regions in proportion to the blood supply. Although not completely diffusible, water is highly diffusible across the blood-brain barrier and most of the water arriving at the vascular bed in the brain will diffuse into the tissue. Later washout of the radiolabeled water from the brain will take place, also in proportion to the perfusion. Thereby it becomes possible to calculate cerebral blood flow. A quantitative calculation is possible; however, in many studies of functional activation only relative changes are recorded. Due to the fast decay of ^{15}O, the radiation dose to the subject investigated is rather low, especially when using a PET scanner in 3D mode (three-dimensional recording with high counting efficiency). It is possible to make about 24 activation studies with a radiation exposure of only approximately two times the yearly background radiation. Since PET relies on radioactive compounds, there are specific ethical limitations to how high a dose a subject can be given within a given period of time. As a result, weight is put on the radioactive property when choosing between compounds in a study.

Another positron-emitting isotope which has been used for functional activation studies is ^{10}C in the form of ^{10}C carbon dioxide (Law *et al*., 2001). The half-life of ^{10}C is only 19 seconds yielding a very low exposure for radiation and thus allowing for up to 64 PET scans with the same radiation exposure as for 12 scans using $H_2{}^{15}O$. The short half-life of ^{10}C also allows repeated measurements with shorter intervals or following the activation during continuous infusion at the tracer. $^{10}CO_2$ has only gained limited use, probably because an even higher time resolution without exposure to radioactivity can be obtained with fMRI. Still, the $^{10}CO_2$ method might have special interest in areas where fMRI is hampered with susceptibility artifacts, as for instance close to the nasal sinuses, such as the orbitofrontal cortex.

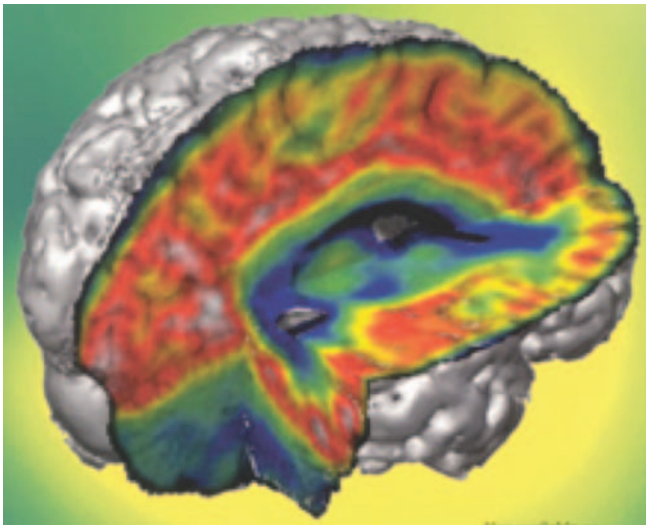


FIGURE A.12 5-HT2A receptor binding as measured with PET and co-registered to a structural MRI image. *Source*: Adams *et al*., 2004.

More recently, advances have been made toward functional imaging of neurotransmission; exciting prospects have recently emerged for *in vivo* monitoring of the brain's own signaling in terms of neurotransmitter release. A prime example is the PET demonstration of competition effects between endogenous dopamine and the radiolabeled dopamine D2 receptor antagonist ^{11}C-raclopride or the SPECT tracer ^{123}I-IBZM (see Figure A.13). Striatal radioligand binding decreased as the dopamine level increased under a successful video game session (Koepp *et al*., 1998). So far, the concept has primarily been used in conjunction with D2 receptor imaging and, in spite of attempts to identify PET tracers sensitive to, e.g. serotonin release (Pinborg *et al*., 2004), a well-suited tracer still needs to be identified.

2.3.1 Image analysis

An image analysis approach frequently used to compare groups is the 'region of interest' (ROI) technique. In this, each subject's image is shown on a visual display unit and a tracker ball or pen is used to outline regions of interest. The mean activity for each region for the experimental subjects would then be compared

[2] An electronvolt (eV) is the amount of kinetic energy gained by a single unbound electron when it passes through an electrostatic potential difference of 1 volt, in vacuum. The kilo-electronvolt (keV) is 1000 eV.

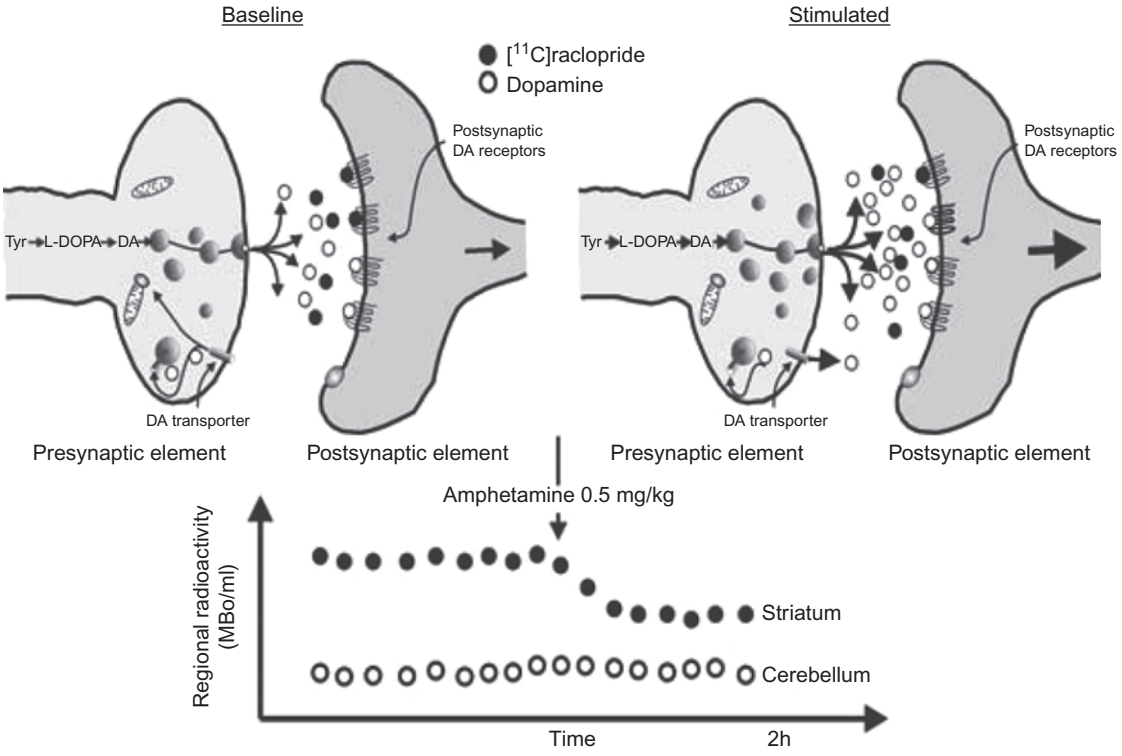


FIGURE A.13 The dopaminergic synapse at baseline (left) and after pharmacological stimulation with amphetamine. Bottom panel shows 11C-raclopride binding levels (in a steady-state approach) as dopamine levels increase. *Source*: Laruelle, 2000.

with that of the controls. The main drawback with this technique is that it takes no account of structural brain differences which might exist between subjects. Using a human operator to decide the boundaries of regions of interest on the functional image requires the assumption that the operator knows where to place the boundaries. On a functional image, the inference that structural boundaries can be identified is obviously a circular one. There are two solutions to this problem. The first is to obtain structural imaging data as well as functional imaging data for each subject. Then, data-processing techniques can be used to 'co-register' the imaging data on a voxel-by-voxel basis, such that a superimposed map for each subject is obtained. The PET image in Figure A.12 shows a 3D rendered image of a co-registered PET and MRI image.

2.4 Magnetic resonance imaging (MRI)

MRI is an imaging technique used primarily in medical settings to produce high quality images of the inside of the human body. It is based on the principles of nuclear magnetic resonance, which is a spectroscopic technique used by scientists to obtain information about the chemical and physical properties of molecules. As such, MRI started out as a tomographic imaging technique – a method for obtaining pictures of the interior of the body. Today, MRI has advanced far beyond this and now represents a battery of different approaches that can measure the structure, function, connectivity and chemistry of any part of the body.

MRI is based on the absorption and emission of energy in the radiofrequency range of the electromagnetic spectrum. The human body is mostly made of fat and water – body tissues that have many hydrogen atoms. As such, the human body consists of about 65 percent hydrogen atoms. These hydrogen nuclei form the very basis for the signal in MRI. A voxel is a volume element that represents a value in 3D space. This is analogous to a pixel, which represents 2D image data. Voxels are frequently used in the visualization and analysis of medical and scientific data. In brain imaging, the brain is divided into a number of voxels and within each voxel one can do different kinds of statistical testing. Each voxel (Figure A.15) in the human body contains one or more tissues. Zooming in on the voxel reveals cells and within each cell there are water

BOX A.3 Altered neurochemistry in psychiatric disease

In a study by Adams *et al*. (2005) patients suffering from obsessive-compulsive disorder (OCD) were scanned for the binding of serotonin in the brain (using the [^{18}H]altanserin binding to 5-HT$_{2A}$ receptors). OCD is a psychiatric condition affecting 2–3 percent of the population worldwide and it is classified as an anxiety disorder. The symptoms include recurrent, unwanted thoughts (obsessions) and conscious, ritualized acts (compulsions), usually attempting to deal with the apprehension generated by the obsessions. OCD is often treated with a selective serotonin reuptake inhibitor (SSRI), a chemical compound that makes serotonin available in the synapse for a longer time.

When comparing a group of OCD patients to an age- and gender-matched control group, Adams and her colleagues found an increased [^{18}H]altanserin binding in the caudate nuclei. This indicates that there are more active 5-HT$_{2A}$ receptors in the OCD brain than in healthy controls. Such an up-regulation of serotonin receptors is suggested to be a compensatory mechanism due to lack of serotonin in OCD patients. The serotonin network being affected includes structures such as the orbitofrontal prefrontal cortex, thalamus, caudate nucleus, and globus pallidus.

The researchers then rescanned the patients after administering SSRI for at least 12 weeks, a treatment that would increase the amount of serotonin available in the OCD brain. The results now showed no difference between the control group and the patient group in the serotonin binding. In other words, there were not more active 5-HT$_{2A}$ receptors in the OCD groups after treatment than in the control group.

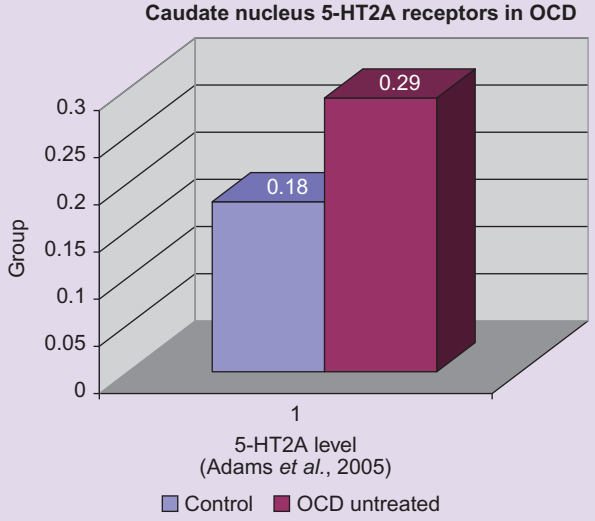


FIGURE A.14 5-HT$_{2A}$ receptor activation level in untreated OCD and healthy controls.

PET studies like these provide important information about the neurochemistry of psychiatric disease and they have extended this understanding by providing new evidence about the neurochemical workings of psychiatric drugs such as SSRIs.

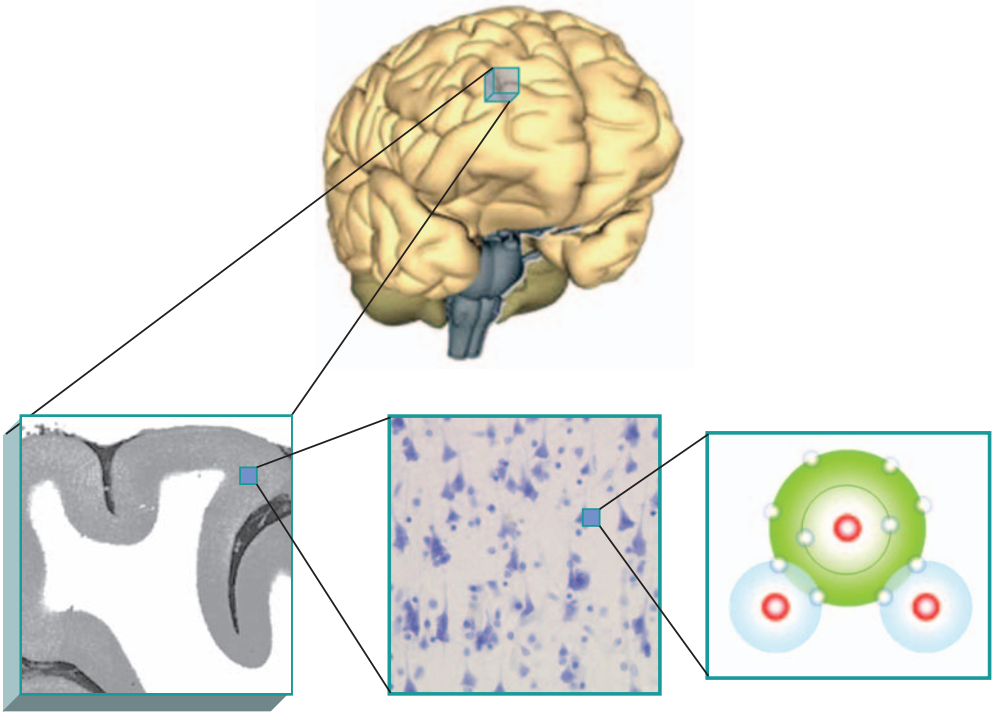


FIGURE A.15 Voxels as minimum boxes of brain space. A voxel of the brain. The voxel is a representation of a volume in three-dimensional space. In the brain, the resolution of the scanner determines how small the voxels can be. Parameters such as higher scanner field strengths increase the spatial resolution and hence the ability to represent separate structures in the brain. The brain voxel extracts the signal from one part of the brain, where the local molecular environment influences the magnetic response. The voxel chosen here is much larger than usual for MRI scans, for illustrative purposes. *Source*: Jones *et al*., 2002.

molecules. Each water molecule consists of one oxygen atom and two hydrogen atoms. If we zoom into one of the hydrogen atoms past the electron cloud we see a nucleus comprised of a single proton.

In a magnetic field, such as the MR scanner, the magnetic orientation of each hydrogen atom is aligned to the magnetic field and spins around this orientation (Figure A.16(b) and (c)). If a brief electromagnetic (radiofrequency) pulse is applied, it temporarily distorts the atom's alignment to the magnetic field (Figure A.16(d)). When the radiofrequency pulse ends, the atoms start to realign to the magnetic field, a process called *relaxation* (Figure A.16(e)). It is during this phase that the atom loses its own energy by emitting its own energy, providing information about the environment. The relaxation occurs in two dimensions: Time-1 and Time-2. The realignment with the magnetic field is termed *longitudinal relaxation* and the time in milliseconds required for a certain percentage of the tissue nuclei to realign is termed 'Time 1' or T1. This is the basis of T1-weighted imaging, which produces the most well-known structural images in MRI. T2-weighted imaging relies upon local dephasing of spins following the application of a transverse energy pulse; this *transverse relaxation time* is termed 'Time 2' or T2.

The T1 and T2 constants provide the basis for most medical imaging. In different parts of the body, such as the brain, different tissues alter the speed in which T1 and T2 relaxation occurs. The three most typical tissues of the brain are gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). The influence of these tissues produces different signal intensities – contrast – that make it easy to distinguish between them. By varying different parameters during scanning, such as the rate and amplitude of the radiofrequency pulse, or the time from excitation to recording, it is possible to highlight different properties of the tissues and their differences.

This can clearly be seen in images that display the difference between T1- and T2-weighted images (Figure A.17). As the images show, a brain tumor that can be hard to see on a T1-weighted image is clearly visible on the T2-weighted image. This is due to the fact that tumors contain more water and hence give rise to

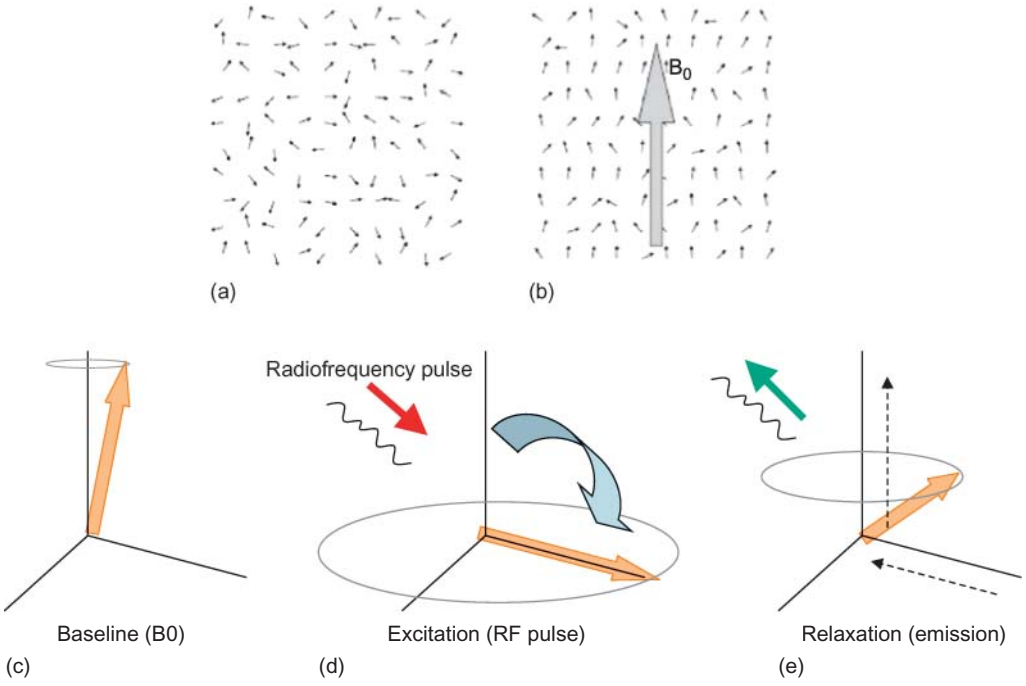


FIGURE A.16 The signal that makes up the MRI. (a) Outside the scanner the atoms are oriented at random in the brain. (b) When a subject is put into the scanner, the atoms align to the magnetic field of the scanner (B_0). However, the alignment is not perfect, since neighboring atoms influence each other. (c) At such baseline, the atom spins along the y-axis, i.e. the B_0 field. (d) When a radiofrequency (RF) pulse is applied the spin of the atoms is influenced and 'pushed' down. This is a state of disequilibrium and during equilibration toward the B_0 field the atom releases energy that it received from the RF pulse. (e) The local milieu of the atom, i.e. whether it is in gray matter, white matter, bone, or cerebrospinal fluid, determines the speed of this *relaxation*. This is the basis of contrast in the MR image and thus what makes it possible to visualize the different tissues of the body.

a larger signal using T2-weighted imaging due to the slower longitudinal relaxation time. Since the longitudinal relaxation is fast in water, the extra water in the tumor produces no extra signal in T1-weighted imaging.

Structural scanning techniques are obvious choices when studying alterations in the brain due to aging, brain injury, or degenerative disorders such as Alzheimer's disease. Based on such imaging of brain morphology (structure), it is also possible to ask questions about how the brain changes structurally as a result of development, aging and degenerative diseases. For example, Jernigan *et al*. (2001) demonstrated age-related changes in different parts of the cortex and cerebellum. By using the structural MRI images and drawing in the anatomical regions, the researchers were able to compare the relative size of these structures across the age range. As Figure A.18 illustrates, there are profound changes occurring in the brain as we age. Furthermore, there is a non-linear relationship between age and brain volume, something that contradicted the earlier views about the aging brain. Finally, a significant finding in this literature has been that there are regional differences in how the brain ages.

2.4.1 Functional MRI

While T1- and T2-weighted images are superior at imaging the structure of the brain, MRI also offers ways to measure different functions of the brain. In general, there are two main approaches: BOLD fMRI and perfusion MRI. While the BOLD approach relies on a complex series of events that couple brain activation to vascular changes and the relative level of regional oxygenated blood, perfusion MRI measures the cerebral blood flow (CBF) or cerebral blood volume (CBV).

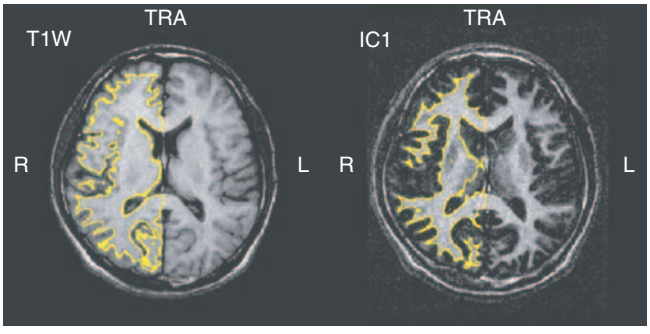


FIGURE A.17 T1- and T2-weighted images. Note that the brain tumor can be hard to see on a T1-weighted image, while it is easy to see on the T2-weighted image – it is the round dark spot on the left of the brain image on the right. *Source*: Nakai *et al*., 2004.

BOLD fMRI is the most used and well-known way to assess brain activation with MRI. Brain activation changes the relative concentration of oxygenated and deoxygenated hemoglobin – blood with or without oxygen, respectively – in the local blood supply. While oxygenated blood is *diamagnetic* and does not change the MRI signal, deoxygenated blood is *paramagnetic* and leads to a drop in the MRI signal. If there is more deoxygenated blood in a region it therefore leads to a drop in the BOLD signal and more oxygenated blood in the region leads to a higher signal. The BOLD response can be thought of as the combination of four processes (Figure A.19):

1. *An initial decrease* (dip) in signal caused by a combination of a negative metabolic and non-metabolic BOLD effect. In other words, when groups of neurons fire they consume more oxygen. When this happens, the local level of oxygenated blood drops and there is relatively more deoxygenated blood in that area. In addition, there is also a dilation of the blood vessels, which further increases the negative BOLD effect.
2. *A sustained signal increase* or positive BOLD effect due to an increased blood flow and a corresponding shift in the deoxy/oxyhemoglobin ratio. When the neurons go back to a lower level of activation, their increased consumption of oxygenated blood drops. At the same time, influx of new oxygenated blood is increased due to the previous demand. As the blood oxygenation level increases, the signal continues to increase. This drop in demand of oxygenated blood, combined with a delayed supply of oxygenated blood, leads to a dramatic 'overshoot' of the relative amount of oxygenated blood. This abundance leads to the main effect of the BOLD signal.
3. *A sustained signal decrease* which is induced by the return to normal flow and normal deoxy/oxy hemoglobin ratios.
4. *A post-stimulus undershoot* caused by a slow recovery in cerebral blood volume.

The 'initial dip' is thought to be the measure most closely related to the neural activation, since it relates to the first drop in signal intensity due to consumption of oxygenated blood. However, the signal changes at this stage are so small that they are mostly detectable by the use of extra strong MRI scanners, which are both expensive and not yet generally approved for human testing. It is therefore the second phase – the

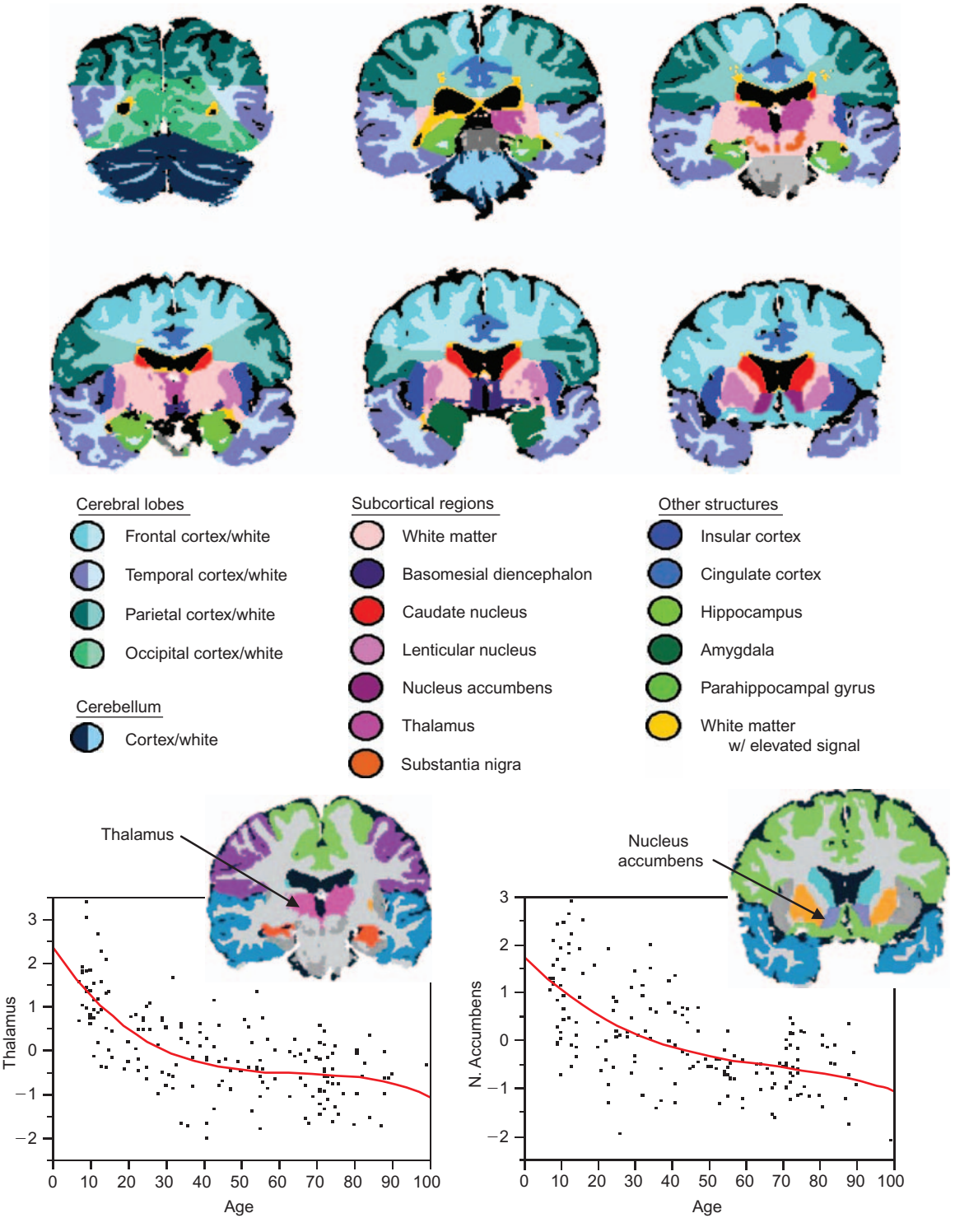


FIGURE A.18 The brain ages differently in different brain regions. *Top*: Example of structural boundaries of the brain drawn as Regions of Interest. Note that the slices consist of both gray and white matter separately; white matter is presented with a lighter color. All white matter voxels that show elevated signal in a group of elderly relative to younger adults are shown in yellow. *Bottom*: Age-related changes in two regions of the brain in the age range 10–100 years, the thalamus and nucleus accumbens (indicated by arrow). Two major effects can be seen. First, both structures seem to have three time-related phases: (1) a precipitant loss of volume in both structures during adolescence and into young adulthood; (2) a flattening out and relatively stable state until late adulthood; (3) a late adulthood loss of volume. Second, the two structures show different trajectories in loss of volume. *Sources*: *Top*: Jernigan *et al*., 2001; *bottom*: Jernigan, with permission.

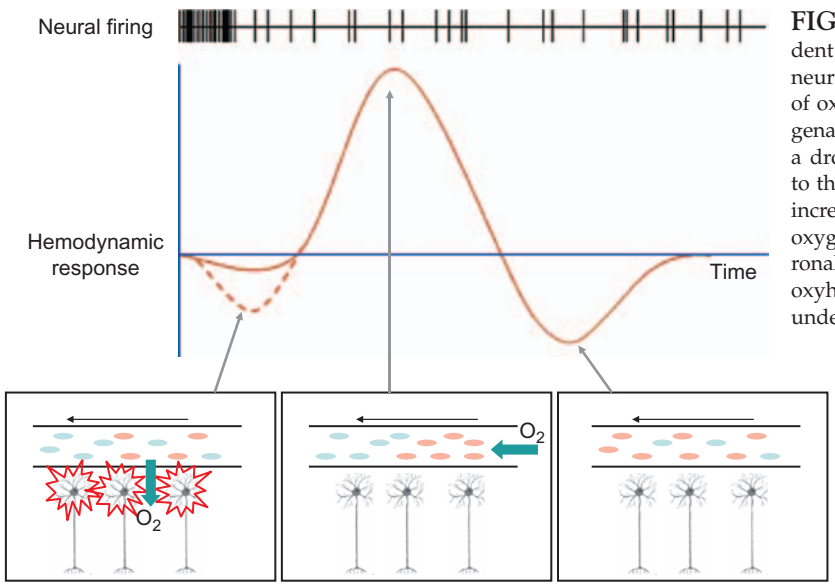


FIGURE A.19 The blood oxygenated-level dependent signal simplified in four steps. Step 1: increased neural activation leads to an increase in the consumption of oxygen from the blood, leading to a lower level of oxygenated blood and more deoxygenated blood, leading to a drop in the BOLD signal. Step 2: the vascular response to the increase in oxygen consumption leads to a dramatic increase in new, oxygenated blood at the same time as the oxygen consumption drops due to decreased levels of neuronal activation. Step 3: a normalizing of flow and deoxy/oxyhemoglobin levels (not shown). Step 4: a post-stimulus undershoot caused by the slow recovery of blood volume.

sustained signal increase – that is used in most BOLD fMRI studies. This signal is an indirect measure of neural activation, as it is the result of a delayed vascular overshoot of oxygenated blood, as a response of demand for oxygenated blood in a region. Although the BOLD response is an indirect and delayed measure of neural activation, it has been shown to have a time resolution at the millisecond scale. In addition, the method has a very high spatial resolution at below 1 mm resolution. With recent technical advances, the resolution has become even smaller than this, bringing MRI to the sub-millimeter scale.

There are different ways in which a study can be conducted using fMRI. In general, there are two main design categories – block designs and event-related designs. Following PET studies, the *block design* was the most used design in the earliest days of fMRI. Typically, a block design consists of a presentation of stimuli as blocks containing many stimuli of the same type. For example, a block design may be used for a sustained attention task, where the subject is instructed to press the button every time he or she sees an X on the screen among other letters. Typically, blocks are separated by equally long periods of rest, although one may design block experiments without rest. A block design could be used if we were interested in seeing the difference between encoding of the identity versus the position of objects (Figure A.20).

In an *event-related design*, stimuli are presented in a random or pseudo-randomized order. Here, individual stimuli of various condition types are presented in randomized order, with variable stimulus onsets. This approach provides a means to look at different trial-relevant changes such as correct versus error responses. An event-related paradigm therefore lies closer to a traditional psychological experiment and it allows *post-hoc* analyses with trial sorting (accuracy, performance, response time, etc.). This design is more efficient, because the built-in randomization ensures that preparatory or anticipatory effects (which are common in blocks designs) do not confound event-related responses. An example of an event-related paradigm can be seen in Figure A.21.

When do you choose to use either a block or event-related design? In general, one can say that if you want to study state-related processes (as in 'encoding state' versus 'retrieval state'), then a block design would be the best choice. However, if you want to study item-related processes (as in correct versus incorrect responses), an event-related design is optimal. In certain experimental setups, it is possible to combine block and event-related designs, making it possible both to track overall differences in cognitive states, as well as being sensitive to differences from instance to instance.

When considering the experiment design, another important issue concerns the states that are compared. There are several different contrasts one can choose to make. In some cases, especially in older neuroimaging studies, a comparison is made between a specific task and a rest period (see Figure A.20). Today, it is more usual to compare two or more active states. In general, we can distinguish between within-subject comparisons and between-subject comparisons. In *within-subject*

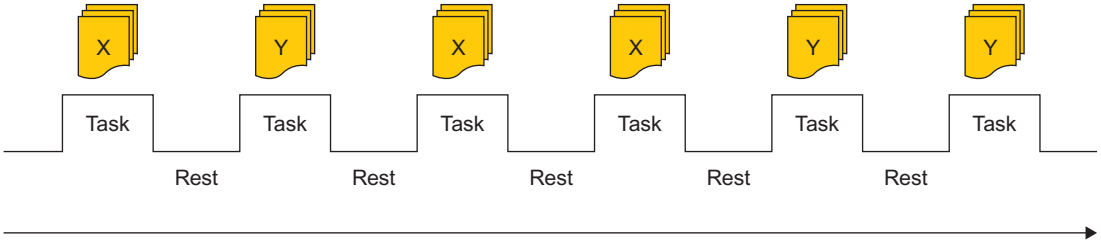


FIGURE A.20 The block design. Intervals of separate trials (X and Y) are separated by periods of rest. Note that the order of X and Y trials is random. In such a design, X trials could be 'reading letters' while Y trials could be 'reading numbers'.

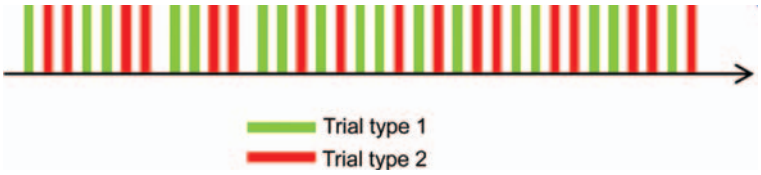


FIGURE A.21 The event-related design. Unlike the block design the event-related design focuses on individual trials. Hence, the order of stimuli is much more random and is good for use in psychological designs where we do not want the subject to be able to predict the order of stimuli. An example paradigm could be to present stimuli at very brief durations and ask for each stimulus presentation whether the subject has seen the stimulus. Responses will vary according to the duration of the stimulus, as well as endogenous processes (e.g. inattention). The subjects are not able to predict their next response (or stimulus experience).

BOX A.4 The BOLD nature of conscious perception

What is the neural fate of stimuli that are consciously perceived? How do these processes compare to stimuli that are processed but not experienced? Are there situations where we get vague impressions that something was presented yet we are unable to describe it? If so, how does the brain work under such perception?

The neural correlates of consciousness have been studied for well over a decade using neuroimaging tools. Such findings converge on the idea that conscious perception – as opposed to unconscious perception – involves a widespread network of areas in the brain (Baars, 2002b). This network is comprised of prefrontal and parietal cortices and very often temporal areas. It is also speculated that the spreading of information within this network occurs through cortico-thalamo-cortical loops, i.e. signals initiating in the cortex spread to widespread connections through the thalamic nuclei.

Recently, behavioral studies have documented that the usual distinction between conscious and unconscious perception has to be reconsidered (Ramsøy and Overgaard, 2004). If subjects are allowed to make use of more elaborate responses about their experiences, they consistently acknowledge that some of their experiences can best be described as vague. This condition can be thought of as the detection of something being presented without the ability to identify what it was. One question thus becomes: how does this experience relate to conscious and unconscious perception? Just as important, one may ask if there is a different neural substrate for such experiences.

In a study by Christensen *et al*. (2006), this question was examined by presenting backward masked visual stimuli at different durations while scanning subjects with fMRI. This paradigm leads to different levels of experience of the stimuli and, from the experience of previous behavioral studies (Ramsøy and Overgaard, 2004), subjects were allowed to use a non-dichotomous rating scale to report experiences as not seen, vague, and clear experiences. Simple visual objects were presented for brief durations up to about 100 milliseconds. For each stimulus the subjects rated how clearly they had seen the object. This made it possible to compare unique activations for neural processes underlying clear and vague experiences.

First, the comparison between reports of *clear and no experience*, i.e. the traditional difference between conscious and unconscious perception, led to the previously seen widespread network of brain areas. This included the parietal and prefrontal cortices, the temporal lobe (fusiform gyrus), well known for its role in object perception (Figure A.22(a)). Conscious perception was also shown to involve large amounts of the thalami in both hemispheres.

(*Continued*)

As such this finding supports a 'globalist' account of consciousness in the brain, stating that conscious perception requires a widespread network of brain areas.

What, then, about vague experiences? When comparing reports of vague and no experience the researchers found activation in much of the same network only not as widespread, as they had found in conscious perception (Figure A.22(b)). By comparing states of clear experience to vague experiences, it was possible to identify the areas that are involved in turning detection into identification (Figure A.22(b)). From this, it seems that when we detect something, or have a vague feeling of seeing something, we use a widespread network of brain areas, with special activity found in the prefrontal cortices. If this vague perception changes into a fully conscious perception of a stimulus, the activity in the network increases dramatically both in spread and amplitude. As such, this study by Christensen *et al*. has provided novel and important new data to our understanding of conscious and unconscious perception.

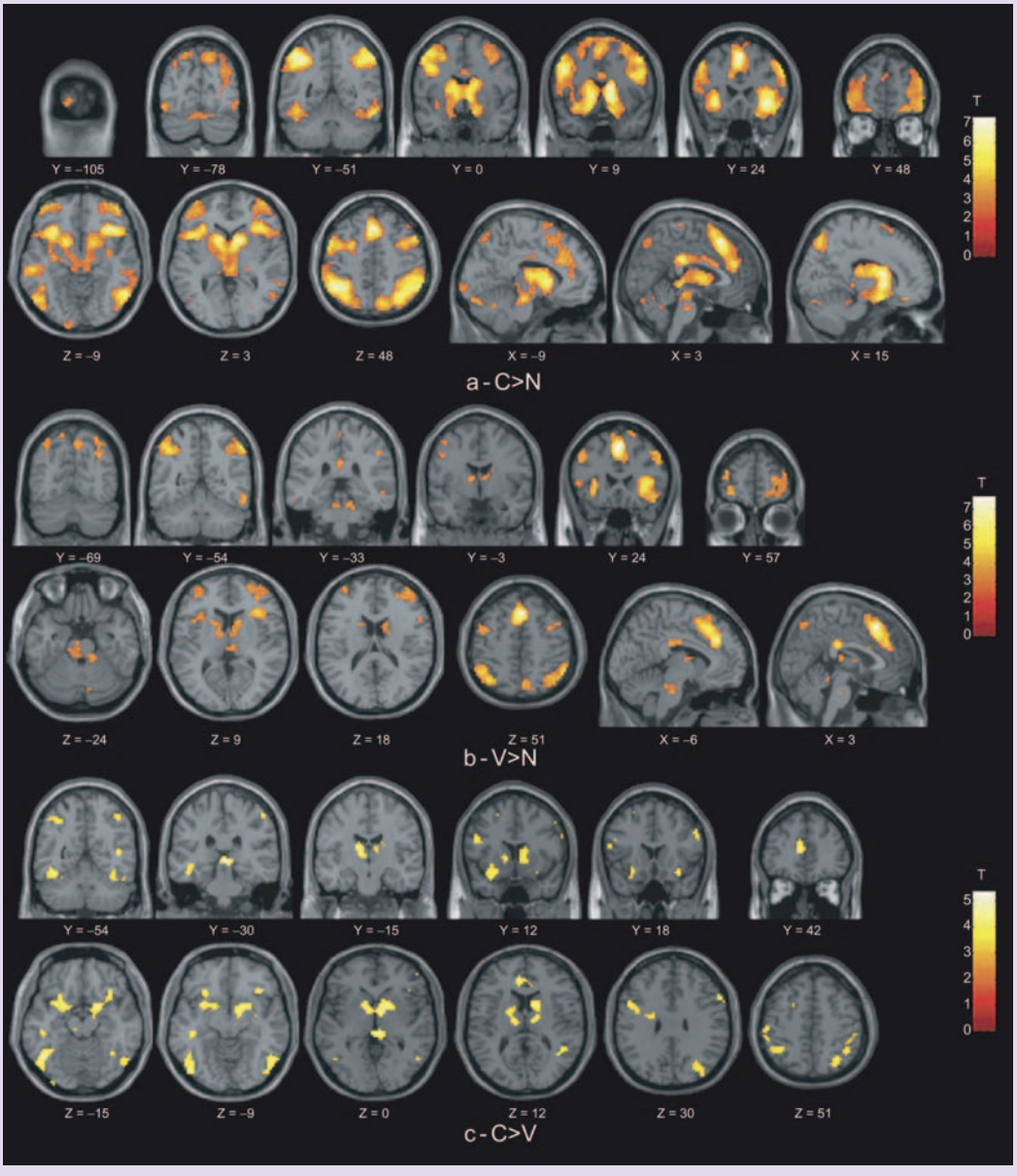


FIGURE A.22 An fMRI study by Ramsøy and colleagues (Christensen *et al*., 2006) shows differing networks of activation for visual stimuli that are clearly perceived versus vaguely perceived. Top two rows (a) show the significant activity for clear perception (C) compared to no perceptual experience of the stimulus (N). Next two rows (b) show the activity for vague or glimpse-like (V) perceptual experience compared to N. *Source*: Christensen *et al*., 2006.

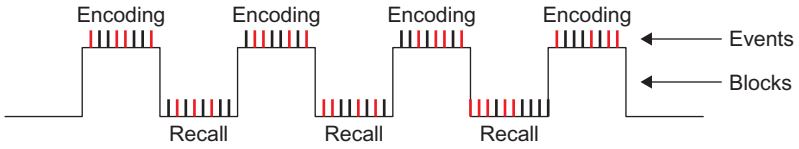


FIGURE A.23 Combining blocked and event-related designs is possible under certain circumstances. Here, analysis can focus either on the block level, e.g. comparing encoding and recall activation, or it can use the behavioral data from a recall phase to look at the neuronal activation within the encoding blocks for the instances of successful encoding only (i.e. ignoring data for stimuli that were later forgotten). *Source*: Thomas Ramsøy, Daniela Balsler, and Olaf Paulson, with permission.

TABLE A.1 Different designs for neuroimaging studies

Within-subject designs	**Examples**
Different processing states	Reading words aloud versus self-generation of words
Compare effects of contents during same state	Encoding of faces versus houses
Longitudinal study	Test-retest of the same cognitive function • Learning effects • Aging effects • Disease effects (only for diseases that changes over time)
Between-subject designs	**Examples**
Manipulation effects	Attention processing in ecstasy abusers versus non-users
Training effects	Effect of juggling training on motor cortex activation
Patients and controls	Working memory function in schizophrenic patients versus healthy controls
Different groups of patients	Encoding in patients with Alzheimer's disease versus patients with semantic dementia

designs, a comparison can be made between two different processing states, between different contents during a given state, or as effects of time. *Between-subjects designs* allow for studying group effects in a number of ways, including comparison of patients and healthy subjects, between different groups of patients, or between two groups who have been manipulated (e.g. trained) differently. A list of some possible designs is presented in Table A.1. In this way, it is imperative to pay attention to what comparisons are being made in a given experiment.

When studying the effects of one condition, one must always contrast that to some other condition to achieve any meaningful data. Let us demonstrate this with a study on the perception of facial expressions. In a standard emotion task in neuroimaging (Del Ben *et al*., 2005), subjects are asked to look at images of different faces. Half of the faces are female and the subject's task is to report whether the face is a male or a female. At the same time, the faces also vary according to what kind of emotion is expressed. The faces can either be neutral or aversive (e.g. sad or frightened). During the experiment, our main focus is on the difference between seeing aversive and neutral faces. During the analysis of the data, we first determine when the aversive and the neutral faces were shown. We then determine the signal intensities for each of these periods and look at the mean signal intensity for neutral and aversive faces, respectively. The mean signal and distribution in the brain for each condition are shown in Figure A.24. If we are interested in identifying areas that are involved in the processing of aversive faces, we take the mean activity during aversive stimuli and subtract the mean activity of all neutral stimuli. In this way, all activations that are common for both conditions, including primary visual processing and rudimentary face perception, are cancelled out. What we end up with is where in the brain we see specific rise (or fall) in activation when the subjects see aversive faces.

BOLD fMRI is probably the most used measure of brain activation today. It has demonstrated its utility in every aspect of cognitive neuroscience and is continuously being developed as a research tool. With increasing technological advances the method will lead to a better understanding of the temporal and spatial workings of the mind and brain.

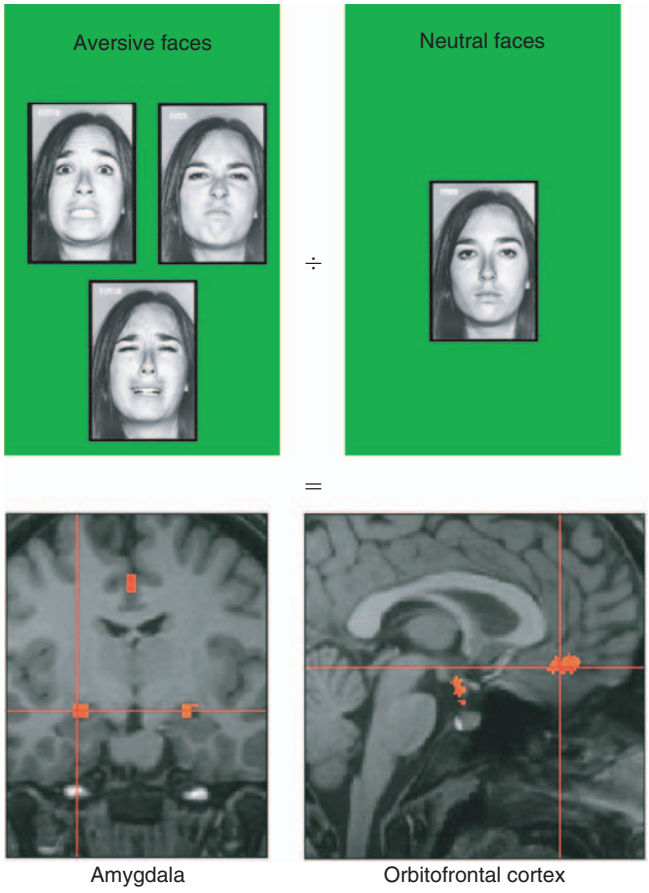


FIGURE A.24 fMRI for aversive emotional faces. Looking at aversive faces activates emotion areas of the brain. In a series of different face stimuli, some faces are aversive (e.g. frightened, sad, and showing repulsion) and others are neutral. If we subtract the activity associated with neutral faces from aversive faces, we get neural signal that is selective for looking at aversive faces. Here, bilateral amygdala and orbitofrontal activation can be seen in an individual subject using this contrast. *Source*: Del Ben *et al.*, 2005.

2.4.2 *Arterial spin labeling (ASL)*

By altering the magnetic properties of the blood flooding into the brain, an MRI measurement can also be made sensitive to the blood perfusion in the brain. A technique called *arterial spin labeling* uses this idea by 'labeling' the blood in the carotid artery by applying a brief radiofrequency pulse. This alters the magnetic properties of this part of the blood. As this blood continues to flood into the brain, it makes it possible to measure the relative change in magnetic susceptibility of a region of the brain, or the entire brain. A perfusion-weighted image can be performed by subtracting a baseline brain image with no magnetized blood from a brain image with magnetized blood. In this way, one can measure the blood perfusion in a region of the brain and it is also possible to compare perfusion images between groups; see Box A.5.

2.4.3 *Other specialized MRI sequences*

Diffusion tensor imaging (DTI) and tractography

MRI can also be used to measure the movement of water molecules over time. In a free and unconstrained (isotropic) environment, water will diffuse equally in all directions, also known as Brownian movement. If you measure the diffusion in this medium, the resulting image will be a sphere. If water is put into a more constrained (anisotropic) environment, however, it cannot diffuse freely but can only move along the structures that it is physically limited by. For example, in a glass of water, the water in the middle can move freely in all directions. The movement potential of one water molecule is equal in all directions. However, if you put a drinking straw into the water, the movement potential of the water molecules within that tube is dramatically limited. If you now measure the water diffusion within this tube, it is no longer circular or equipotent, but an oblong sphere (Figure A.26).

In biological matter such as the brain, the water diffusion is significantly limited. However, there is a systematic difference between gray and white matter. While gray matter has little inner structure in the sense of limiting water diffusion, white matter consists of fibers that constrain the diffusion in some directions more than others. Just like putting one or more straws into the glass of water hinders water from moving through the straw walls, neuronal fibers constrain water diffusion across, but not along, the fiber direction (see Figure A.26(b)). Connections between brain areas occur as bundles of fibers (axons). By using diffusion tensor imaging, it is possible to measure the relative direction and coherence of these white matter tracts. Thus, DTI can be used to measure white matter changes in neurological disease, but it is also possible to determine how a selected area is connected to other brain areas by following the fibers from the selected region, a method called *fiber tracking*. The use of DTI in a healthy brain can be seen in Box A.6.

MR spectroscopy

Magnetic resonance spectroscopy (MRS) is closely related to magnetic resonance imaging. Both techniques use the magnetic properties of atomic nuclei to get information about a biological sample. However, there is a crucial difference: while MRI measures the spatial distribution of magnetization, MRS measures

BOX A.5 ASL of Alzheimer's disease and mild cognitive impairment

Although significant cognitive changes can be detected at an early stage of Alzheimer's disease (AD), including memory deficits, more physiological changes also occur in the brain. By studying the perfusion of blood in these patients, it is possible to see what areas show a general lower metabolism or flow of blood. In such a study, Johnson *et al*. (2005) used arterial spin labeling to compare the perfusion levels in a group of AD patients to that of healthy old subjects and subjects suffering from mild cognitive impairment, a pre-diagnostic syndrome where at least a subgroup show a high conversion rate to AD.

The researchers found a significant decrease in perfusion in the AD group, compared to the control group, in a number of regions in the parietal cortex, posterior cingulate cortex, and frontal cortex. At a lower statistical threshold, the MCI group demonstrated a lower perfusion in the right inferior parietal lobe, the same place where the largest effect was seen in the AD group. This study demonstrates that perfusion scanning using ASL can be used to detect differences between groups at different stages in Alzheimer's disease.

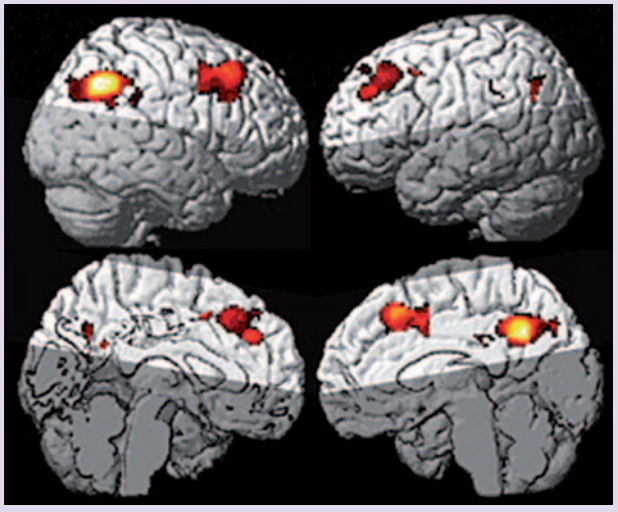


FIGURE A.25 ASL in Alzheimer's disease. *Source*: Johnson *et al*., 2005.

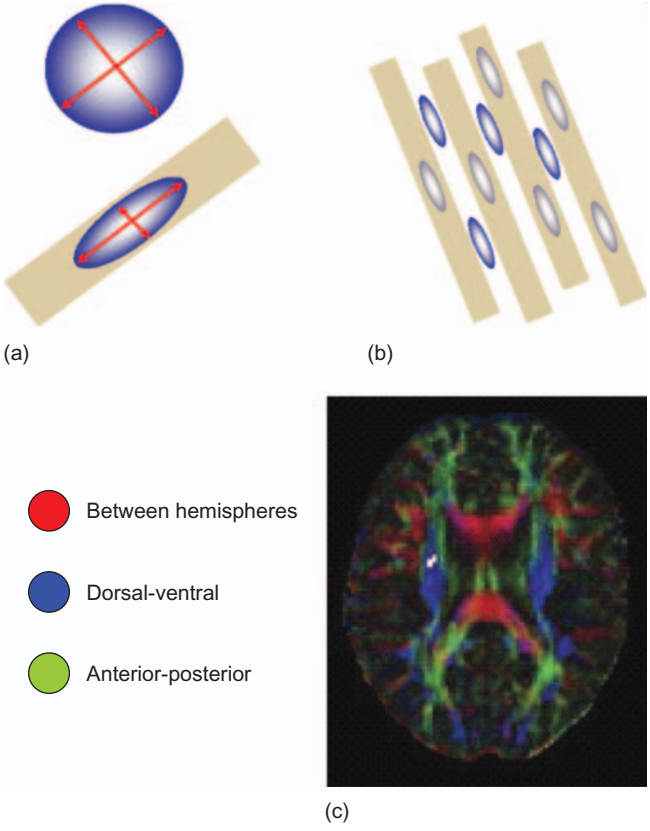


FIGURE A.26 Diffusion of water depends on the local environment. (a) In the free and unrestricted medium (i.e. a glass of water) water can diffuse freely. The diffusion is *isotropic*; it has the potential to move in all directions. If the water molecule is physically restricted it can no longer move freely in any direction. This diffusion is *anisotropic*; it cannot move in any direction. In a medium of fibers such as the brain's white matter (schematically shown in (b)) water molecules are highly restricted by the axonal fibers. In this way, it is possible to visualize the fiber tracts of the brain and furthermore to estimate the integrity (homogeneity) of white matter in a given region. (c) Such visualization produces the typical colored DTI brain image that displays different trajectory trends in regional white matter.

the amount of signal from each chemical environment (chemical or molecular distribution). In other words, MRI allows one to study a particular region within an organism or sample, but gives relatively little information about the chemical or physical nature of that region. MRS, which is an NMR method, provides a wealth of chemical information about the same region. The frequency distribution is called a

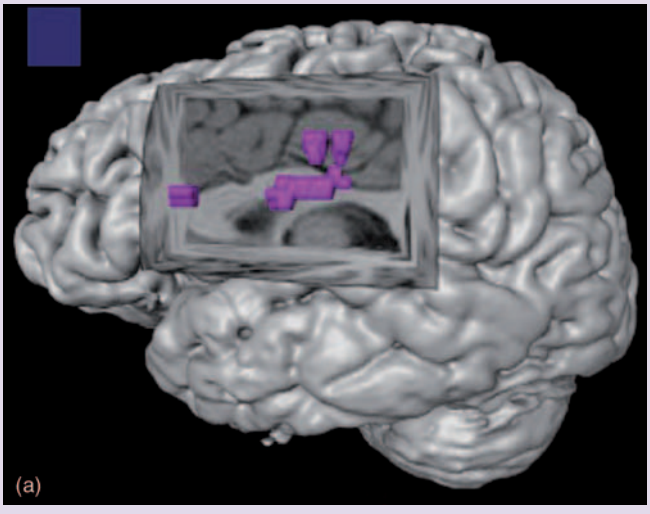
BOX A.6 Reading ability and brain connectivity

Reading is a complex cognitive skill that is the result of coordination between many different brain regions. In order for such a communication between brain regions to occur, there must be physical contacts between these areas. This can be either through direct connections between two or more areas, or indirect connections through one or more additional areas. Although many studies using functional imaging address the cooperation between such areas, they do not provide direct evidence about the structural connections that are present in the brain to support this cooperation.

In a study by Beaulieu and colleagues (Beaulieu *et al.*, 2005), this was addressed by studying the brain connectivity in children with diverse reading abilities. By comparing white matter connectivity and integrity changes and reading ability in children, Beaulieu discovered five white matter areas that were good indicators of the children's reading ability.

The researchers went on by looking at the different connectivities in these areas. By using each white matter area as a 'seed point', the researchers could detect and visualize the connectivity of each cluster. These were generally ordered in three groups: one going between the front (anterior) and back (posterior) ends of the brain; one group of left-right oriented fibers; and one traveling from the upper (superior) to the lower (inferior) parts of the brain.

In this way, Beaulieu and colleagues were able to determine both the white matter regions that are important in reading skills in children and, at the same time, say which pathways these areas represented. Following these discoveries, it is now possible to generate more specific hypotheses about the neural substrate for reading skill acquisition, how these areas could be functionally connected, and to test them using other methods, e.g. fMRI.



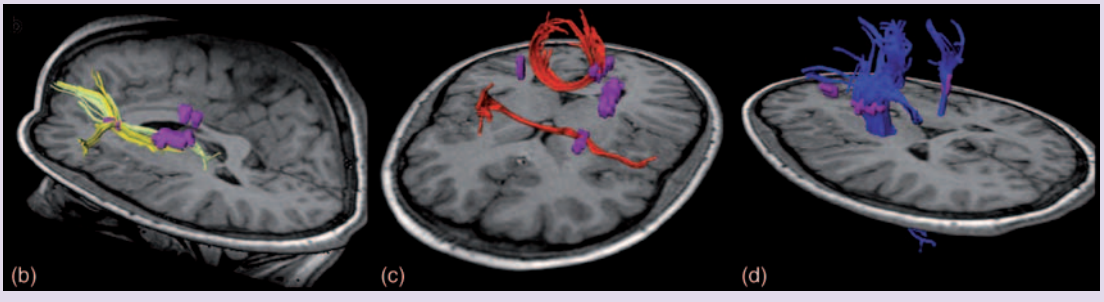


FIGURE A.27 Connectivity patterns in the brain were investigated by Beaulieu and colleagues (2005) using DTI. (a) Shows the brain areas (in purple) selected for investigation. Four were in the left hemisphere and one in the right. (b) Shows white matter tracts (in yellow) for the preselected regions that have an anterior-posterior (front to back of the brain) orientation. (c) Shows white matter tracts (in red) for the preselected regions that have a left-right orientation. (d) Shows white matter tracts (in blue) for the preselected regions that have a superior-inferior (top to bottom of the brain) orientation. *Source*: Beaulieu *et al.*, 2005.

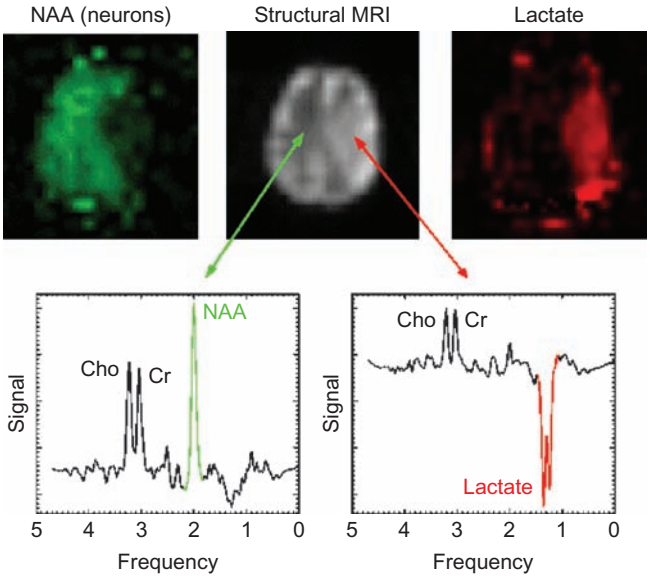


FIGURE A.28 Spectroscopic MRI detects chemical differences in brain pathology. *Left*: (green), the healthy part of the brain shows normal NAA levels (green peak), while on the left-hand side this NAA level has diminished, while lactate has a significantly altered (red) drop. *Source*: Courtesy of Lars Hanson, Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital, Denmark.

spectrum and is analogous to the optical spectra of substances which are responsible for their visible colors. In this way, MRS can measure the chemical composition in a given region of the brain. MRI and MRS can be combined to provide the spatial distribution of chemical compounds as shown in Figure A.28. This figure shows the spectrum from a region of the brain and the corresponding chemical distribution of this region. If you compare this healthy area with an area from a diseased brain region, you can see some dramatic changes. First, from the healthy hemisphere it is possible to see that the *N*-acetylaspartate (NAA) signal is the highest of all molecular compounds. The NAA is a marker of mature axonal white matter in the living brain (Bjartmar *et al*., 2002). By contrast, this is precisely the same signal that drops dramatically if we measure the same area in the lesioned hemisphere. Even without such dramatic effects, MRS can be used to study degeneration of brain tissue in diseases such as multiple sclerosis (De Stefano *et al*., 2005), stroke (Saunders, 2000), and Alzheimer's disease (Falini *et al*., 2005), but also the effects of substance abuse (Magalhaes, 2005; Reneman *et al*., 2006).

2.5 MRI – a tool for the future

With its superior spatial resolution and multiple uses, the MR scanner is an indispensable tool in cognitive neurosciences. The advances in MRI come from many directions but, in general, we can speak of two categories of advancements: *technical* and *analytical* tools. *Technical advances* include the production of scanners operating at higher field strengths. Increased field strengths enhance the scanner's ability to record signals. So, by exchanging a 1.5 Tesla (1.5 T) scanner with a 3 T scanner, we get a higher spatial resolution in both the structural images as well as the functional images. While 3 T or 4 T is the current high-field standard in scanning subjects and patients, scanners are already available at higher field strengths such as 7 T and 11 T. Scanning the cortex at 7 T or higher field strengths has now demonstrated the possibility to make out the different layers of the cortex (Fatterpekar *et al*., 2002; Zhao *et al*., 2006). This is important not only because we get a higher resolution for studies already performed, but it will also generate whole new ways to study the brain, and our ideas about its workings.

Advances in field strengths are complemented by other areas such as improvements in the apparatus that generate the magnetic pulse, or the receiver that records the signal. Such ongoing improvements are likely to make significant contributions to the possibility of scanning the brain with increasingly higher resolution and sometimes invent novel ways to acquire the data. While these advances promise a better resolution, they are also associated with specific problems. For example, the higher field strength that produces better signal-to-noise ratio in most parts of the brain leads to greater loss of signal in other areas. Since the BOLD signal (see previously) relies on the relative amount of oxygenated blood in an area, areas with oxygen that are not part of the brain influence the signal in that area. The medial temporal lobe and ventral prefrontal cortex both lie close to the nasal air cavities. As a result the BOLD signal in these brain regions is corrupted by the non-brain areas filled with oxygen. When moving from field strengths of 1.5 T to 3 T, this became a problem that needed to be addressed. fMRI activation data from the hippocampus, amygdala, and orbitofrontal cortex were distorted by a loss of signal at 3 T. To overcome this problem, studies now use specialized sequences that minimize the artifacts in these areas. However, when moving from the standard 3 T or 4 T to 7 T or higher field strengths, these problems re-emerge. Only new advancements in noise reduction methods can solve these problems.

The other general area of advance is *software improvement*s. In a few years, the field of neuroimaging has seen a significant expansion in the number of ways to analyze data. Many of these improvements

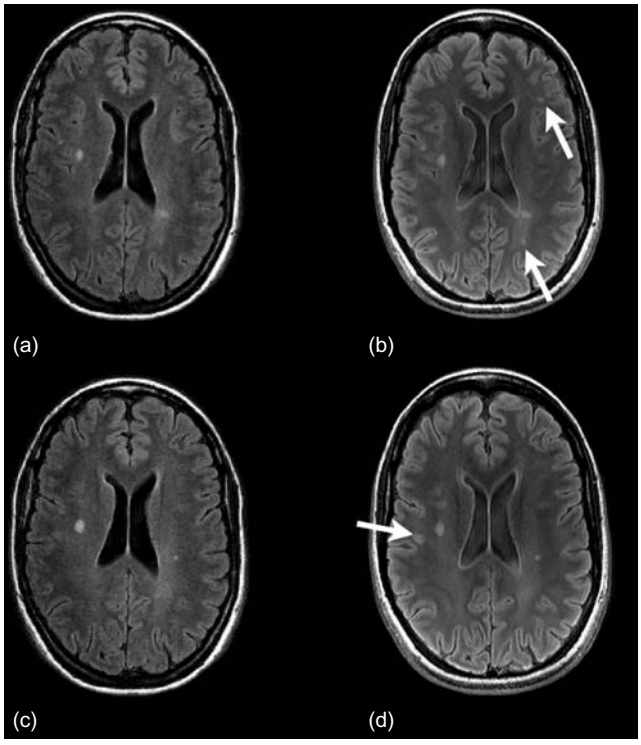


FIGURE A.29 Increased field strength leads to higher resolution images. By comparing the image of the same subject on both a 1.5 T and a 3 T scanner it is possible to see the resolution increase. Here, the pathological changes occurring in sclerosis are best seen using 3 T (b and d) while several lesions are not even detected at 1.5 T (a and c, see arrow in d). All image acquisitions were done with the injection of a contrast agent, gadolinium. *Source*: Nielsen *et al*., 2006.

are not isolated to MRI alone, but are relevant to most or all neuroimaging approaches. While the early days of fMRI neuroimaging analyzed trial blocks, later advances, such as the event-related paradigm, has led to new analytical tools. One such is the dynamic causal modeling (DCM) analysis of neural activation patterns. In general, DCM is a way to analyze how activations across the brain occur at the same time or are caused. There are two main ways to analyze such data. An analysis of the *functional connectivity* focuses on correlations between brain areas. For example, one can ask whether there is a contingent relationship between activation in the hippocampus and the dorsolateral prefrontal cortex (DL-PFC) during an encoding task. Here, one can get an estimate of how correlated two (or more) areas of the brain are – in other words, the relative activation strength between two or more areas. The second kind of analysis is to look at the *effective connectivity* between areas. Here, one tries to move beyond mere correlation and estimate the relative cause and effect relationship between areas. In our example of hippocampus and DL-PFC, we move beyond asking how correlated the regions are and now how one area is causing the other to activate. Today, both approaches are being developed continuously and are increasingly being used in the analysis of neuroimaging data. However, since they rely on specific experimental design and data sampling, only paradigms specifically tailored to the analysis can be used.

2.6 Optical imaging

Optical imaging is a quite recent addition to the brain imaging toolbox. A laser source of near-infrared light is positioned on the scalp. A bundle of optical fibers is used as detectors and placed a few centimeters away from the light source. The detectors record how the path of light from the laser source is altered, either through absorption or scattering, as it traverses brain tissue. This information is used in two ways. First, it can measure the concentration of chemicals in the brain by measuring the absorption of light in an area. Second, it can provide information about more physiological properties of the brain that are associated to the level of neuronal firing. This is done by measuring the scattering of light, which is an indicator of swelling of glial cells and neurons. In this way, optical imaging provides a simultaneous measure of both the source and time course of neural activation within an area of the brain.

In a study using optical imaging, Sato and colleagues (Sato *et al*., 2005) studied the activity of somatosensory cortex in the pre-surgical planning stage of patients with brain tumors or epilepsy. As with previous findings in the human and non-human animal literature, Sato *et al*. found that the organization of the somatosensory cortex consisted of neighboring response areas, for example, the fingers, and that the areas demonstrated a certain amount of functional overlap. This is illustrated in Figure A.30. It is also noteworthy to consider the relation between these findings and the study of brain plasticity in phantom limb sensation presented in Box A.2. This study also demonstrates that optical imaging has a potential use in pre-surgical planning.

3.0 MULTIMODAL BRAIN IMAGING

Neuroscience today rests on a number of different imaging techniques (modalities) and we have only mentioned the most prominent here. Each approach continues to provide novel findings that contribute to our understanding of the brain and our cognitive apparatus. But, as Figure A.1 demonstrates, each imaging technique has its

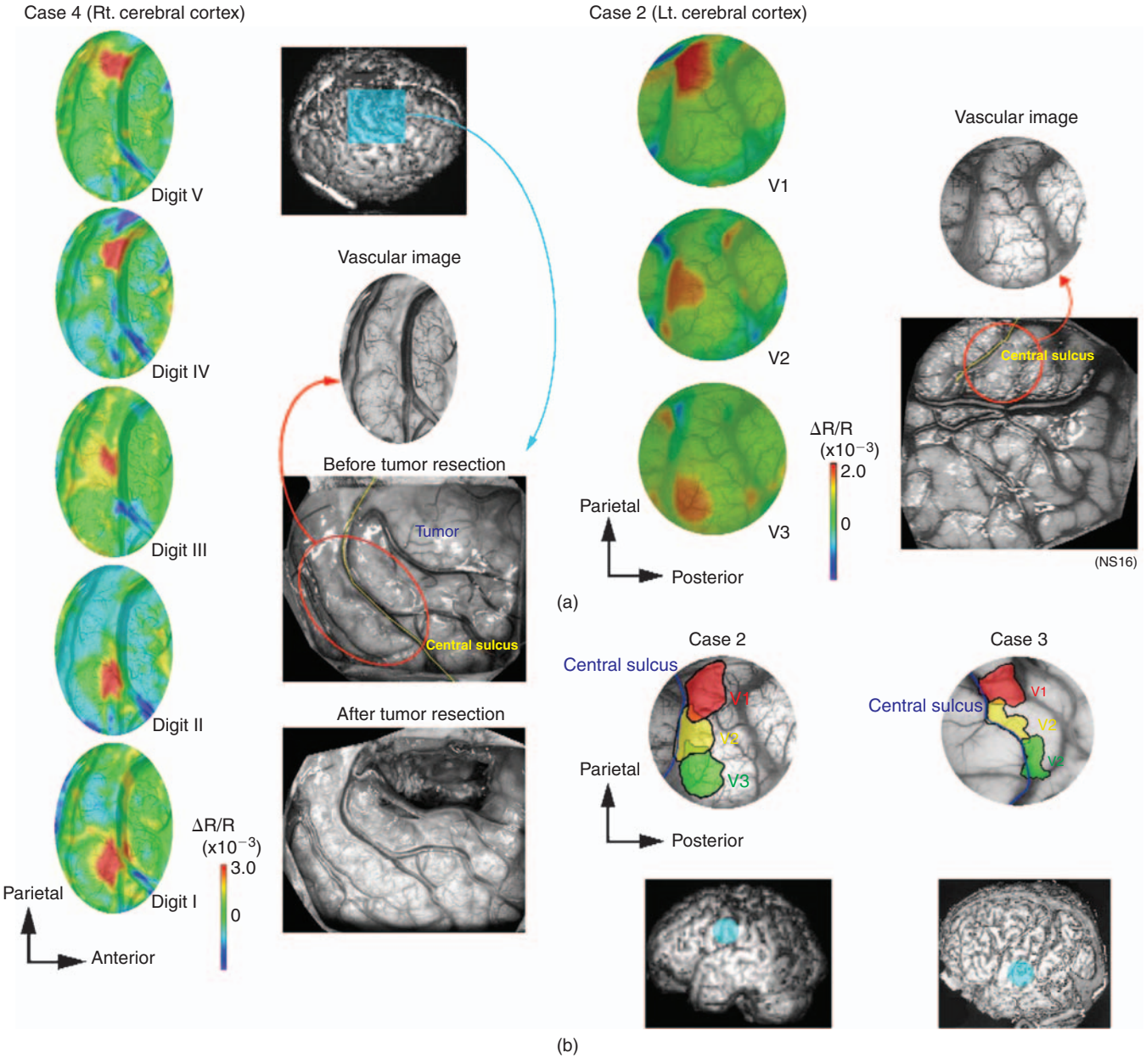


FIGURE A.30 Optical imaging: The cortex responds visibly to stimulation. Intrinsic optical responses to stimulation of the digits from the left somatosensory cortex of a 47-year-old patient. The detected optical responses are illustrated in added color superimposed on a vascular image. *Source*: Adapted from Sato *et al.*, 2005.

strengths and weaknesses, especially in terms of its relative spatial and temporal resolution. An obvious solution is therefore to compare findings from studies using these different imaging approaches. However, since each method is different from the rest, we will never get identical results. Instead, what we get is added information about our area of interest. For example, if our study focuses on subjects reading a text aloud, we can compare the results from EEG and fMRI. In this way, we can get a better understanding of both the localization of areas that are responsible for text reading (fMRI) and, at the same time, get results about the millisecond-to-millisecond changes in activation levels during the task (EEG).

Imaging modalities can be compared in many ways. In addition to the comparison of the results in different studies, an often-used approach is to combine imaging techniques more directly. A PET study will most often co-register its findings to a standard MRI or CT structural brain. The same is actually done with fMRI images: the activation images are co-registered to the

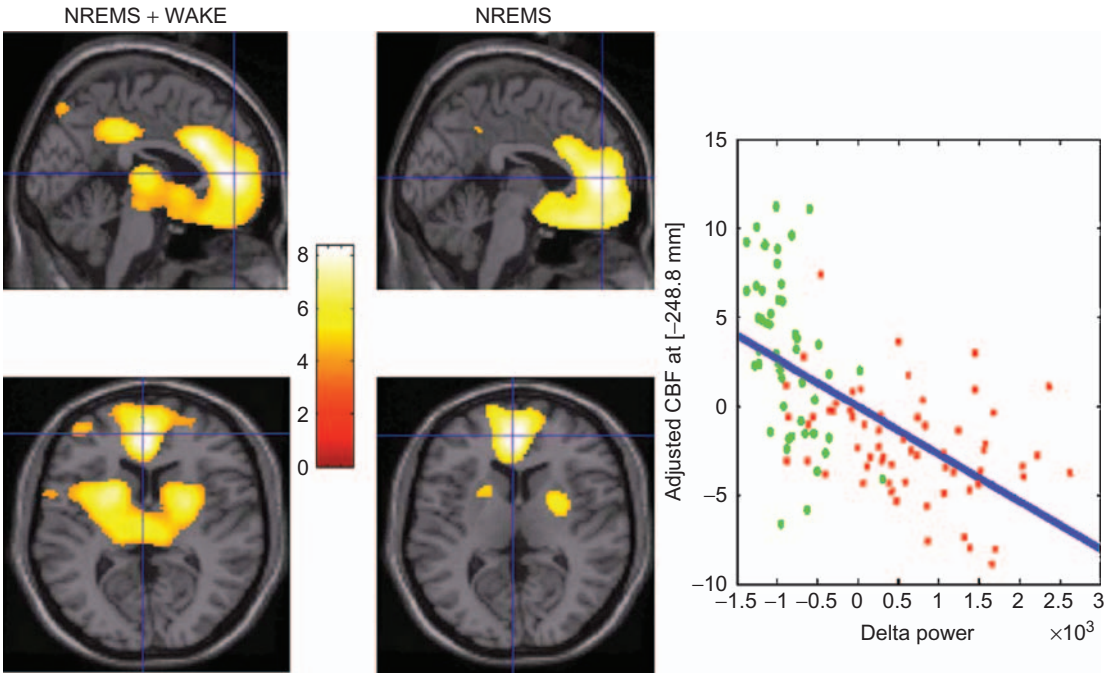


FIGURE A.31 The brain substrate for delta power during non-REM sleep. The image shows regional changes in the cerebral blood flow as a function of delta power during non-REM sleep. The activations are shown on a mid-sagittal slice (left) and different axial slices (right). *Source*: Dang-Vu, 2005.

structural scans. This process gives us the opportunity to have a better ability to see where in the brain our changes are found. The activation images in themselves bear too little information about the localization of the activations to be meaningful.

3.1 Simultaneous imaging from different sources

While most comparisons are done on images that have been recorded separately, for example, the PET scan and the structural MRI scan, it is also possible to record and co-register results from recordings that have been done simultaneously. For example, Dang-Vu and colleagues (Dang-Vu *et al*., 2005) used combined EEG and PET to study the contributions of brain areas in different levels of sleep. The EEG and PET recordings were done simultaneously while the subjects were sleeping. The researchers then identified the unique stages of sleep from the EEG patterns and focused on delta activation during non-REM (NREM) sleep and compared this to REM sleep and normal wakefulness (see Figure A.31). The researchers found a negative correlation between delta power and regional cerebral blood flow in the ventromedial prefrontal cortex, the basal forebrain, the striatum, the anterior insular, and the precuneus. These findings thus hint about areas that vary in delta activation according to our level of awareness.

Similarly, Laufs and colleagues (Laufs *et al*., 2003) combined EEG and fMRI measurements in the study of subjects at rest. The study of 'resting state' must be seen as controversial, due to the fact that neither the mind nor the brain can be seen as being at 'rest' at any time. Laufs *et al*. assessed the different patterns of activity occurring within phases in which subjects were 'at rest' and found that the resting phase consisted of 'intertwined yet dissociable dynamic brain processes' in the EEG. In other words, the neuroimaging studies imply that the brains of subjects at rest are doing different things at different times within the rest period. Furthermore, the researchers were able to make out separate neural networks underlying EEG bands, such as the alpha and beta band activity.

It should be noted that there is a substantive difference between combining EEG with PET and with fMRI. While the PET scanner does not induce artifacts that are insurmountable for the EEG, the MR scanner produces artifacts in the EEG so substantial that attempts until only recently have been unsuccessful at such a combination. One approach has been to read the EEG from people between fMRI runs and, in this way, assess the state of awareness, e.g. whether they are sleeping or awake. Through proper noise filtering

it has now become possible to filter out the scanner artifacts and make the EEG data useable even from within the fMRI scanner. In this way, it has become possible to combine the high temporal resolution from the EEG with the high spatial resolution in the MRI. Still, the filtering of artifacts is seen as problematic – we may see a significant loss of true signal, while some residual artifacts (even from the filter applied) can occur. Combined measures such as the EEG/fMRI must therefore still be interpreted with caution.

3.2 Imaging genetics

Within the area of multimodal brain imaging, new important steps are taken to combine our understanding of how genes make up your mind. Genes act at the molecular level in the body and thus act as the very building blocks of neurons. In this way, individual differences in the genetic makeup can influence the workings of the brain in significant ways.

A natural variation in the promoter region of the serotonin transporter gene (called 5-HTTLPR) has been linked to alterations in serotonin transcription as well as serotonin uptake. Individuals who have two copies of the long (l) variant have a higher concentration of the serotonin transporter mRNA and therefore have greater serotonin uptake in comparison to individuals who have two versions of the short (s) variant. These subjects have a relatively lower concentration of the transporter and, as an effect, relatively greater synaptic serotonin levels. Hence, the genetic makeup you might have in this area influences how much or little serotonin you have available in the brain. Just looking at your genetic makeup with respect to the serotonin transporter gene, it is now possible to predict the level of active serotonin in any given person.

By applying such a combination of neuroimaging and genotyping, Hariri and colleagues (Hariri *et al.*, 2002) demonstrated that the type of genetic makeup had implications for the response of the amygdala to pictures of facial expressions (Figure A.32). Subjects with the short genetic version demonstrated elevated levels of amygdala activation, presumably caused by a higher concentration of serotonin in these subjects. This genetically driven difference in amygdala excitability might contribute to the increased fear and anxiety typically associated with the short genetic version. As such, the study by Hariri and colleagues is a powerful demonstration about what can drive the individual differences in how the brain works (Figure A.33). Today, many researchers hold the view that this area of 'imaging genetics' holds the promise to give significant new insights into the workings of the brain and mind.

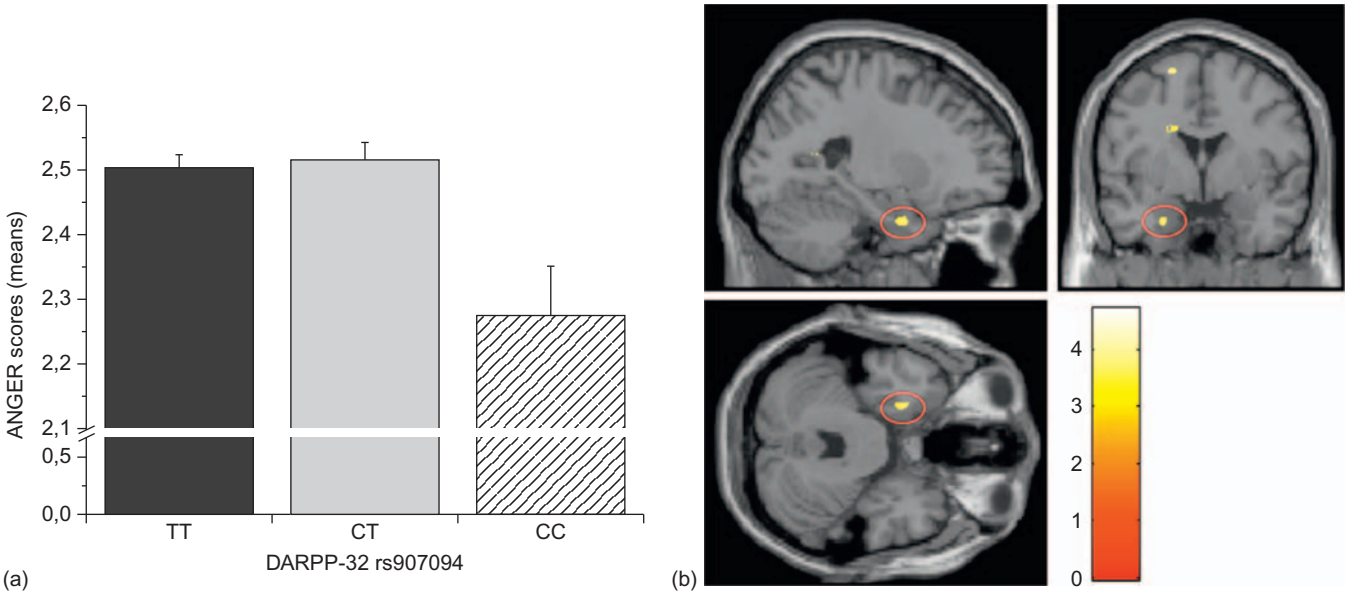


FIGURE A.32 Genes, anger, and the amygdala. (a) Self-reported anger scores (on a scale called ANGER) are higher in males with high levels of specific TT and CT base pair sequences of the DARPP-32 gene, compared to CC sequences in the same DNA regions of the same individuals. (b) An MRI shows that in these subjects the gray matter volume (the neural cell bodies) of the left amygdala is significantly lower than in the control group. *Source*: Reuter *et al.*, 2009.

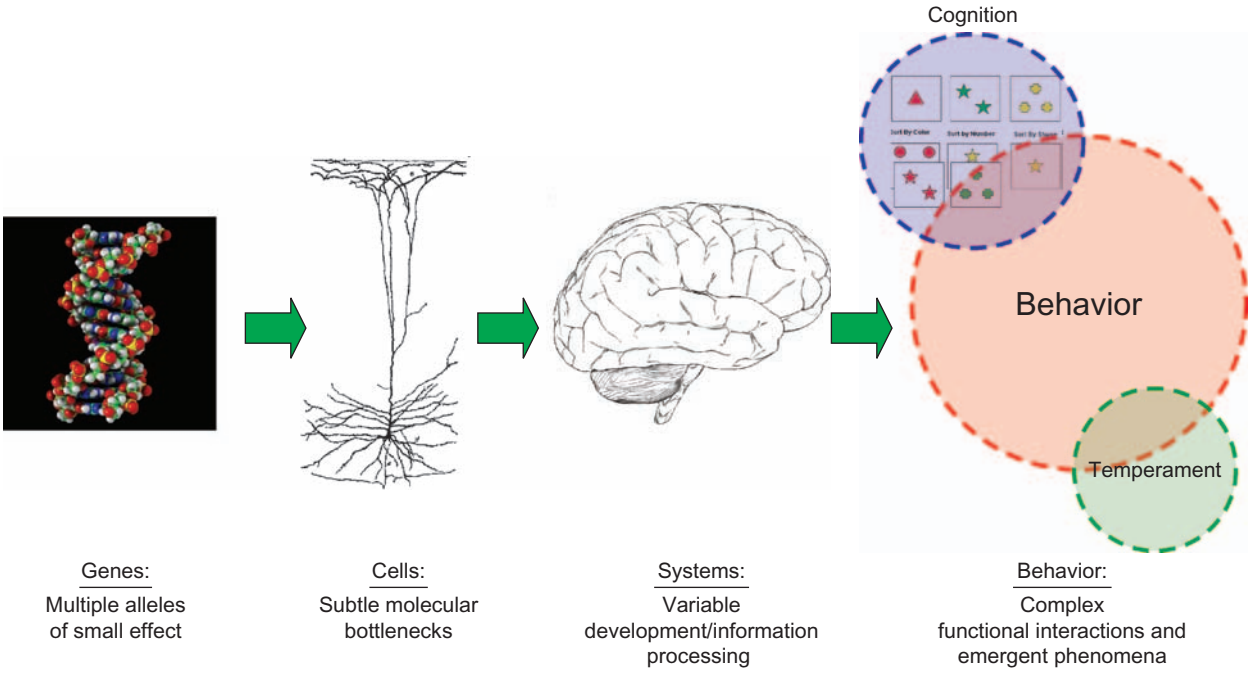


FIGURE A.33 Multileveled understanding of brain and mind. Four levels of understanding the mind and its brain. Imaging genetics allows for the estimation of genetic effects at the level of brain information processing, which represents a more proximate biological link to genes as well as an obligatory intermediate of behavior. *Source*: Adapted from Hariri *et al.*, 2006.

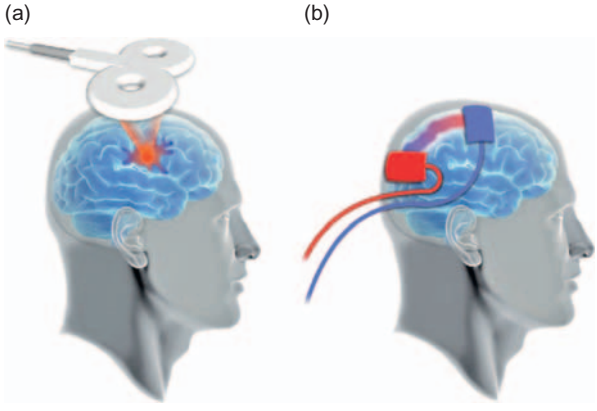


FIGURE A.34 (a) TMS. When researchers operate a TMS coil near a participant's scalp, a powerful (• 2 T) and rapidly (• 300 ms) changing magnetic field passes painlessly through skin and bone. Because the strength fo the magnetic field falls off very rapidly with distance from the TMS coil, it can penetrate only a few centimeters and this means that only superficial areas of the brain are most effectively stimulated. The induced electric field causes electric current in nearby neurons, thus stimulating targeted regions of the cortex. (b) tACS. This method relies on application of alternating currents through an electrode. Electrical currents are applied constantly at low intensities (1 mA) over period of time in the order of seconds, to achieve changes in cortical activity. The waveform of the stimulation is sinusoidal and different frequencies can be used during stimulation (up to 250 Hz). *Source*: Thut & Miniussi, 2009.

Transcranial magnetic stimulation (TMS)

Based on the findings from different imaging methods, one will have a better understanding of the relationship between regional brain activation and cognition. However, these studies most often suffer from being correlational: they often only imply a relationship between activations and cognition. Imagine that in a given task, you find that three regions seem to play important roles. But in order to go beyond these findings, you may wish to study the effects of lesions to these regions. Patient lesions are always a valuable source for performing such tests, but lesions rarely follow tight anatomical boundaries or functional activations. Therefore, using a method that is reversible and that influences the gross operations of small regions of the brain is attractive.

Transcranial magnetic stimulation (TMS) is one such method. In TMS, rapidly changing magnetic fields (electromagnetic induction) are used to induce weak electric currents in the brain (Figure A.34). Although the exact nature of the operations of TMS are not yet fully understood, researchers now typically

divide between two kinds of TMS: single/paired pulse TMS (s/pTMS) and repetitive TMS (rTMS).

In s/pTMS, pulses cause populations of neurons in the neocortex to depolarize and discharge an action potential. If applied to the primary visual cortex, the excitation of this region will make the person experience small flashes of lights (phosphenes). If applied to the motor representation of the hand, one can elicit hand movement, or measure muscle tightening in the hand.

Similarly, s/pTMS can be used to grossly inhibit activation in a particular region of the neocortex. For example, by applying TMS pulses to the temporal lobe region bilaterally, Overgaard and colleagues (2004) demonstrated changes in consciousness of visual stimuli, but not in the ability to guess correctly the property of the stimuli.

In this way, TMS can be used to induce temporary and reversible "lesions" in healthy individuals. This method can be used to temporarily disrupt the function of a particular region of the brain. If this affects task performance it may be deduced that this part of the brain was involved with the task at that particular time point.

The second TMS method, repetitive TMS, produces effects that last longer than the period of stimulation. By applying repeated sequences of TMS pulses, it is possible to grossly increase or decrease the excitability of corticospinal or corticocortical pathways. Although the mechanisms involved in rTMS are not fully understood, it has been discovered that the level of excitability depends on the intensity of stimulation, coil orientation, and frequency of stimulation. It has been suggested that rTMS works through changes in synaptic efficacy akin to long-term potentiation (LTP) and long-term depression (LTD) (Fitzgerald *et al.*, 2006).

In a recent study, Babiloni and colleagues (2007) demonstrated that rTMS to the ventral parietal cortex affected both attentional processes and subjects' sensory consciousness. This suggested that the ventral parietal cortex plays a functional role on visuospatial attention and primary consciousness.

In recent years, studies have also discovered that rTMS applied to specific regions may lead to neurophysiological changes. For example, studies have demonstrated that rTMS to the prefrontal cortex induces changes in dopamine levels of the striatum and caudate nucleus (Strafella *et al.*, 2001, 2003), possibly by acting through corticostriatal networks.

Through its diverse uses, TMS is today a method that is still gaining in popularity with scientists. In addition, the method has demonstrated some promise in the treatment of depression and other mood disorders and in Parkinson's disease.

4.0 CONCLUDING REMARKS

Neuroimaging has grown into one of the most important approaches to our increased understanding of the human brain and mind. Advances within each modality – be it optical imaging, EEG, or fMRI – rapidly change ways in which data can be analyzed and even the way we are posing our questions. Continuing innovations, both within hardware and software, make any prediction of the future of neuroimaging hazardous. However, some trends are very likely to continue, including the continuing increase in higher resolution in all modalities and new ways of combining data from different modalities.

We must keep in mind what we are really studying. The study of the human mind and its brain is founded on the very building biological blocks of our body: our genes. Our genes determine how and when our brain develops and it is thus the recipe for our mind that we should seek to understand. In order to do this we need to understand the levels at which we are working to understand ourselves. Here, let us distinguish between four levels. The first level is the genetic and how we understand how genes make up the recipe for cellular components such as proteins and transmitters. Second, we must understand how single neurons work and how they collaborate in networks. Third, we can study the brain to see morphological and functional factors influencing thought. Finally, we can study how effects at any of the previous levels have an effect on our thought, behavior, and even personality.

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Glossary

acetylcholine (**Ach**; uh-see-tel-KO-leen): A neurotransmitter in the central and peripheral nervous system. See Chapter 16.

acetylcholinesterase (**Ache**; uh-see-tel-KO-leen-ES-ter-ayze): An enzyme that deactivates acetylcholine, to clean up the synapse.

acoustical analysis (uh-KOO-sti-kul uh-NAL-ih-sus; Greek *akoustikos* = of hearing): The process of interpreting physical sound energy, whether linguistic, musical, or sounds in the environment (as in a door slamming or a car starting). See Chapter 11, 'Introduction'.

action potential (AK-shun po-TEN-shul): In neurons, an electrochemical signal beginning near the cell body and traveling down the axon to the synaptic terminal. Also called a 'spike' or 'neuronal firing'. See Chapter 3, 'Introduction'.

adenosine (uh-DEN-oh-seen): An inhibitory neurotransmitter that is believed to promote sleep and suppress waking arousal. See Chapter 16.

adrenaline (uh-DREN-uh-lin; from Latin, *ad-* = on top of; *renes* = kidney; -in = protein): Also called epinephrine, it is a peripheral hormone and brain neurotransmitter. As a circulatory hormone it is released by the adrenal gland, located on top of the kidneys, and prepares the body for fight or flight. See Chapter 16.

affective blindsight (uh-FEK-tiv BLIND-site; Latin *affectus* = emotion): An inability to understand emotional facial expressions. See Chapter 13, 'The Fear System'.

agonist (AGG-uh-ist; Latin for competitor). A molecule that binds to a neural receptor, thereby increasing the chance that the postsynaptic neuron will fire. See Chapter 16, 'Remembering the Words'.

alpha waves (AL-fa WAY-vz; first letter of Greek alphabet): A regular electromagnetic wave detected in the brain or on the scalp, and apparently reflecting the activity of large populations of neurons. Alpha waves have a frequency of 7.5 to 13 Hz and originate predominantly from the occipital lobe during periods of waking relaxation with the eyes closed. Conversely, alpha waves are decreased when the eyes are open, as well as by drowsiness and sleep. See Chapter 4, 'A Range of Useful Tools'.

amino acid (uh-MEE-no AE-sid): A constituent part of a protein molecule. Amino acids are critical to life, and have a large variety of metabolic roles. All amino acids contain both an NH_3 (amine) and a COOH (carboxyl) group. See Chapter 16.

amnesia (am-NEE-zhuh; from Greek *a-mn-sia* = not memory): A loss of memory. Two types are anterograde (a loss of memory after the time of the brain injury) and retrograde (a loss of memory before the time of the brain injury). See Chapter 9, 'Amnesia'.

amygdala (uh-MIG-da-la; from *amygdale* = almond): The amygdalas are two small, almond-shaped masses of neurons located inside the tips of the temporal lobes. They are considered part of the limbic system and play major roles in emotions like fear and trust, as well as in learning. See Chapter 1, 'Some History, and Ongoing Debates'.

antagonist (ann-TAG-uh-nist; Latin for competitor): A molecule that binds to a receptor and blocks or inhibits its activity. See **agonist.**

anterior (ann-TEER-ee-er; from *ante* = in front of): Located in front of something. See Chapter 1 and the Mini-Atlas on the inside front cover.

anterior cingulate cortex (an-TEER-ee-er SIN-gyu-lut COR-teks; from Latin *ante* = before, in front of; Latin *cingulum* = girdle; Latin *cortex* = bark): The frontal part of the cingulate cortex. The anterior cingulate cortex is involved in executive functioning. See Chapter 2, 'The Central Executive'.

anterior commissure (an-TEER-ee-er KA-mih-shur; from Latin *ante* = before, in front of): A large bundle of nerve fibers connecting the two cerebral hemispheres. See Chapter 5, 'Introduction'.

anterograde amnesia (AN-teh-ro-grayd am-NEE-zhuh; from New Latin *antero-* = forward; Greek *a-mnēsia* = not memory): A form of amnesia in which events after the brain injury are not encoded in long-term memory, although events may be recalled from the period before the injury. See Chapter 9, 'Amnesia'. See **retrograde amnesia**.

aphasia (AY-PHAY-zha; from, *a* = without; Latin *phasia* = speech): A loss of language function due to brain injury, such as damage to Broca's area, for speech production, or Wernicke's area, for speech understanding. See Chapter 1, 'Some History, and Ongoing Debates', and Chapter 7, 'Speech Perception'.

apparent motion (uh-PAR-ent MO-shun; from Latin *apparēre* = to appear; Latin *movēre* = to move): A form of perceptual filling-in in which the brain creates the illusion of motion when a series of still images are flashed one after the other. See Chapter 6, 'Linking Brain Activity and Visual Experience'.

arcuate fasciculus (AR-cue-ate fa-SIK-u-lus; Latin for curved bundle): A bundle of axonal fibers, especially the ones connecting Broca's and Wernicke's areas in the left hemisphere. See Chapter 1, 'Some History, and Ongoing Debates'.

area MT: A part of visual cortex that represents visual motion. See Chapter 6, 'Functional Organization of the Visual System'.

array (uh-RAY): 1. A two-dimensional grid of sensory receptors, such as the retina. 2. A two-dimensional grid of higher-level elements in the visual hierarchy. Many 'layered' brain structures can be considered to be such arrays. See Chapter 3, 'Arrays and Maps'.

artificial neural net (ar-ti-FI-shel NOOR-el NET; from Greek *neuron* = nerve): Also known as ANNs or neural models, artificial neural nets are simulated, simplified models of brain functions. Most are relatively small in scale. However, they are important for understanding the principles of neural computation. See Chapter 3, 'Introduction'.

associative process (uh-SO-see-a-tiv PRA-ses; from Latin *ad-* + *sociare* = to join): A process in which one or more sensory and/or response events are linked in the brain. See Chapter 5, 'From 'Where' to 'What': The Functional Roles of Brain Regions'.

attention (a-TEN-shun; from Latin *attendēre* = to stretch out): Selection of some sensory, cognitive, or motor events to the exclusion of others. Attention is often taken to involve a focus on certain conscious events. Also see selective attention. See Chapter 8.

attention deficit (hyperactivity) disorder (**ADD** or **ADHD**; uh-TEN-shun DEF-ih-sit hy-per-ak-TIV-ih-tee dis-or-der): A persistent pattern of impulsiveness and difficulty with sustained attention, with or without a component of hyperactivity. There is some debate whether it is a genuine disorder or a normal adaptation that may be problematic today. It affects 3 to 5% of children around the world and continues into adulthood for 30–50% of those affected. See Chapter 12, 'ADHD'.

attention network task (**ANT**; a-TEN-shun NET-werk TASK): A generalization of the **flanker task**, a tool for studying visual attention. The ANT allows testing of three separate aspects of attention: alerting before an expected signal, orienting to a specific location in space where the target is expected, and executive attention to act against expectations set up by the task. See Chapter 8.

auditory cortex (AW-di-tor-ee kor-teks; from Latin *auditorius* = pertaining to one who hears; Latin *cortex* = bark): The parts of the cerebral cortex involved in processing sounds, such as Wernicke's area and Heschl's gyrus. See Chapter 7, 'The Central Auditory System'.

auditory scene analysis (AW-di-tor-ee SEEN uh-NAL-ih-sus): The process by which the auditory system segments and organizes the listening environment. See Chapter 7, 'Introduction'.

autism spectrum disorders (**ASD**; AW-tizm SPEK-trum dis-OR-der): A range of conditions characterized by deficits in social perception and communication, repetitive behavior, and other symptoms.

autonomic nervous system (**ANS**; aw-to-NOM-ic NER-vus SIS-tem; from Greek *neuron* = nerve): The division of the peripheral nervous system that acts to maintain homeostasis and to regulate rest and activity. Physiological activities controlled by the ANS such as blood pressure and sweating are generally unconscious and nonvoluntary. See Chapter 5, 'From 'Where' to 'What': The Functional Roles of Brain Regions'.

automatic process (au-to-MA-tic PRAH-ses): A highly practiced skill or habit that can be performed with minimal conscious involvement and voluntary effort. See Chapter 3, 'Working Assumptions'.

axon (AK-son): A long, slender branch of a nerve cell (neuron) that conducts electrical impulses away from the cell body. See Chapter 1, 'Some Starting Points', and Chapter 3, 'Introduction'.

Balint's syndrome (BA-lint-s SIN-drome): A brain disorder that is marked by simultanagnosia, the inability to perceive two or more objects at the same time. It may also include an inability to point to a target, and to shift gaze voluntarily. See Chapter 6, 'Brain Areas Necessary for Visual Awareness: Lesion Studies'.

Baron-Cohen, Simon (b. 1958): Autism researcher who proposed that young children develop a **theory of mind** capacity, composed of four skills: detection of intentions of others, detection of eye-direction, shared attention with others, and implicit knowledge about others. See Chapter 14, 'Overview'.

basal ganglia (BAY-zel GAN-glee-uh; from Latin *basis* = step, base; Latin for swelling or excrescence): A large cluster of subcortical structures just outside of each thalamus, involving

motor control, automaticity, cognition, emotions, and learning. See Chapter 5, 'Growing a Brain from the Bottom Up'.

behaviorism (bi-HAY-vyer-ism): A philosophy of psychology proposing that all things organisms do, including acting, thinking, and feeling, should be regarded as behaviors. See Chapter 1, 'The Return of Consciousness in the Sciences'.

beta waves (BAY-tuh WAYVZ; second letter of Greek alphabet): A band of irregular electromagnetic waveforms detected in the brain or on the scalp, and apparently reflecting the activity of large populations of neurons. The beta band has a frequency above 12 Hz and is associated with normal waking consciousness. Low-amplitude beta waves with multiple and varying frequencies often are associated with active, busy, or anxious thinking and active concentration. See Chapter 4, 'A Range of Useful Tools'.

binocular disparity (bih-NOC-u-ler dis-PAR-eh-tee; from Latin *bi-* = two; Latin *oculus* = eye; Latin *disparare* = to separate): The difference in perceived location of an object seen by the left and right eyes, resulting from the eyes' horizontal separation. The brain uses binocular disparity to obtain depth information from the retinal image in both eyes. See Chapter 6, 'Functional Organization of the Visual System'.

binocular rivalry (bih-NOC-u-ler RYE-vel-ree; from Latin *bi-* = two; Latin *oculus* = eye): The alternating perception that occurs when a different pattern is shown to each eye and the brain cannot fuse them into a single, coherent percept. Instead, awareness of each eye's input appears and disappears for a few seconds. See Chapter 6, 'Linking Brain Activity and Visual Experience', Chapter 8. See **bistable perception**.

bistable perception (BYE-STAY-bel per-SEP-shun; from Latin *bi-* = two): Sensory events that alternate between two perceptual interpretations. See Chapter 6, 'Linking Brain Activity and Visual Experience'.

blindsight (BLIND-site): A type of brain damage in which patients can report some visual events with no subjective sense of seeing them, due to impairment of the first cortical area of the visual system, area V1. See Chapter 6, 'Brain Areas Necessary for Visual Awareness: Lesion Studies'.

blood-brain barrier: A barrier between the bloodstream and the tissue of the brain, created by cells that line blood vessels in the brain. It allows the passage of small molecules like oxygen and glucose, while blocking larger molecules. See Chapter 16.

blood-oxygen-level-dependent (BOLD) activity (BLUD OKS-eh-gen LEV-el dee-PEN-dent ak-TI-vi-tee): A magnetically induced physical signal that reflects the flow of oxygen in specific regions of the brain. The BOLD signal is the physical source for functional magnetic resonance imaging. See Chapter 4.

brainstem (BRAYN-stem): The lower part of the brain, connecting to the spinal cord. All major motor and sensory systems pass through it, including the optic and auditory nerves. The brainstem also regulates cardiac and respiratory functions, and maintains conscious waking, slow-wave sleep (SWS), and REM dreams. See Chapter 5, 'Growing a Brain from the Bottom Up'.

Broadbent, Donald (1926–1993): British cognitive psychologist who developed the influential concepts of selective attention and working memory. See Chapter 2, 'Limited and Large-Capacity Functions'.

Broca, Pierre-Paul (1824–1880): A French surgeon who studied a brain-damaged patient with expressive aphasia, the inability to speak, while being able to understand speech. After the patient's death he was able to conduct a post-mortem identifying the damaged region as the left inferior frontal gyrus, now called Broca's area. See Chapter 1, 'Some History, and Ongoing Debates'.

Broca's area (BRO-kas AIR-ee-a): The left inferior frontal gyrus, or its posterior segment, reported by Pierre-Paul Broca in 1861 to be responsible for the deficit of a patient who could not speak, but had preserved speech understanding. Other functions have since been attributed to Broca's area. See Chapter 1, 'Some History, and Ongoing Debates', and Chapter 7, 'Speech Perception'.

Brodmann's areas (BROD-mans AIR-ee-uh): About 100 cortical regions defined and numbered by German neurologist **Korbinian Brodmann**, originally based on the microscopic anatomy of **neurons** in different patches of the cortex. They are still widely used for cortical localization, and Brodmann's areas generally have distinctive functions. See Chapter 5, 'Introduction'.

Buber, Martin (1878–1965): An Austrian-born Jewish philosopher best known for his philosophy of 'I and Thou' dialogue, emphasizing the relationships between conscious persons rather than reducing others to objects. See Chapter 14, 'Overview'.

cell assemblies (SEL uh-SEM-blees): Also called Hebbian cell assemblies, these are active networks of related **neurons** representing some sensory input or similar event. According to Donald O. Hebb's 1949 hypothesis, 'neurons that fire together, wire together', so that simultaneous firing causes the **synaptic** links in a cell assembly to grow stronger. See **Hebbian learning**. See Chapter 3, 'Working Assumptions'.

Central Dogma of Molecular Biology, The: The hypothesis that genetic information flows in one direction only, from DNA to messenger RNA, and then to active proteins. The Central Dogma was first enunciated by Francis Crick in 1958, and has been modified by later discoveries showing numerous causal loops that operate in the reverse direction. However, DNA is still a tightly protected molecule that is rarely altered. However, its expression is constantly regulated – enabled or blocked by epigenetic events. See Chapters 15 and 16.

central executive (CEN-trel eks-EK-yoo-tiv; from Latin *centrum* = center): Brain processes for planning, decision making, abstract thinking, rule acquisition, initiating and inhibiting actions, resolving goal conflicts, and flexible control of attention. These functions relate to **working memory** and tend to involve the **frontal lobes**. See Chapter 2, 'Classical Working Memory' and 'The Central Executive'.

central nervous system (**CNS**; SEN-trel NER-vus SIS-tem; from Latin *centrum* = center; Latin *nervus* = sinew, nerve): The brain and spinal cord. All neurons outside of the CNS are considered to be the **peripheral nervous system** (PNS). See Chapter 5, 'Introduction'.

central sulcus (SEN-tral SUL-cus; from Latin *sulcus* = groove): Also called the central fissure, this fold in the **cerebral** cortex is a prominent landmark of the brain that separates the **parietal lobe** from the **frontal lobe** and the **primary motor cortex** from the **primary somatosensory cortex**. The central sulcus is a clear dividing line between the input- and output-related areas of cortex. See Chapter 1, 'Some Starting Points'.

cerebellum (ser-e-BEL-em; from the Latin word *cerebrum* = brain, cerebellum means 'little brain'): A major region of the brain located just below and to the rear of the occipital lobe of the cerebral cortex. The cerebellum plays an important role in the integration of sensory perception, fine motor control, and sensorimotor coordination. Recent evidence shows cognitive involvement as well. See Chapter 1, 'Some Starting Points', and Chapter 5, 'Introduction'.

cerebral cortex (suh-REE-bral KOR-teks; from Latin *cerebrum* = brain; Greek *cortex* = bark): The outer surface of the great cerebrum, the largest part of the human brain, divided into two symmetrical **cerebral hemispheres**. Most of the cortex has six distinctive cellular layers, containing cell bodies with a gray appearance. But its long-distance nerve cells send out axons to other parts of cortex, to thalamus, and to other brain regions, which become covered with white supportive cells (**myelin**). As a result, a vertical cut of the cortex appears to the naked eye to have a thin, gray outer layer and a white inner mass, called the 'gray matter' and 'white matter', respectively. The cerebral cortex plays a key role in sensory analysis, spatial location, speech perception and production, **memory**, **attention**, emotion, motivation, action planning, voluntary control, thought, **executive functions**, and **consciousness**. See Chapter 1, 'Some Starting Points', and Chapter 5, 'Growing a Brain from the Bottom Up'.

cerebrospinal fluid (**CSF**) (suh-ree-bro-SPEYE-nel floo-id; Latin cerebrum = brain): The internal circulation of the spine and brain. CSF allows for a protected flow of molecules and cells that is not exposed to the blood stream.

cerebrum (suh-REE-brum; Latin for *brain*): See **cerebral cortex**.

chromatin (KRO-muh-tin; Greek chroma = color): The substance of the chromosomes of each cell, including DNA, some RNA, proteins, and regulatory molecules that change the expression of DNA.

chunking: A way to make efficient use of short-term **memory** limitations by condensing large amounts of knowledge into a small symbolic units, rules, or regularities, called 'chunks'. In natural language nouns can be considered to be chunks, since they allow us to refer to large bodies of knowledge by single words. See Chapter 2, 'Limited and Large-Capacity Functions'.

Churchland, Patricia (b. 1943): Canadian-American philosopher of mind who won a MacArthur prize in 1991. Churchland's 'neurophilosophy' argues that popular concepts of mind will need to be revised as we learn more about the underlying brain functions. See Chapter 1, Box 1.2.

cingulate cortex (SIN-gyu-lut KOR-teks; from Latin *cingulum* = belt; Latin *cortex* = bark): A part of the **cortex** on the medial (inner) surface of each hemisphere. It is involved in executive functions, the resolution of conflicting goals, and emotion.

classical conditioning (KLASS-ih-kel con-DI-shun-ing): Also called Pavlovian conditioning. A form of associative learning in which humans or animals learn that an arbitrary stimulus (such as a bell) signals the coming of a biological stimulus (such as food). I. P. Pavlov called these the conditioned stimulus (CS) and unconditioned stimulus (US). If the CS is repeatedly presented just before the US, an animal begins to produce a behavioral response to the CS. Pavlov's proposal that conditional reflexes are the basic unit of all human **learning** is no longer generally believed. However, classical conditioning is widely used in research and is thought to be relevant to learned anxiety disorders and food preferences. See Chapter 13, 'Introduction'.

cognitive neuroscience (KOG-ni-tiv NOOR-o-SI-ens; from Latin *cognoscere* = to know): An emerging integration of two previously separate fields of science, cognitive psychology and neuroscience. Most research in cognitive neuroscience makes use of psychological methods simultaneous with brain activity recording. See Chapter 1, 'Introduction'.

cognitive set (KOG-ni-tiv SET; from Latin *cogn* = to know): A state of mental preparedness for some event or action. See Chapter 12, 'A Closer Look at Frontal Lobe Function'.

computed tomography (kom-PYOO-ted tom-OG-reh-fee; from Latin *computare* = to consider; Greek *tomos* = slice; Greek *graphein* = writing): Abbreviated as **CT**. Physiological recordings in which a three-dimensional image of a body structure (such as the brain) is constructed by computer from a series of slice images. See Chapter 4, 'Introduction'.

confabulation (kon-fab-yoo-LAY-shen; from Latin *fabula* = story): A neurological symptom in which false memories or perceptions are reported with no intention to lie. See Chapter 9, 'Memories Are Made of This'.

connectionism (keh-NEK-shun-ism; from Latin *com-* + *nectere* = to bind together): The study of artificial or biologically based neural networks. See Chapter 3, 'How Neural Arrays Adapt and Learn'.

consciousness (KON-shes-ness; from Latin *con* = together; *scientia* = knowledge): Awareness, wakefulness. **Consciousness** implies being sensitive and responsive to the environment, in contrast to being asleep or in coma. Synonyms

include *explicit cognition* and *focal attention*. See Chapter 1, 'Some History, and Ongoing Debates' and 'The Return of Consciousness in the Sciences'; and Chapter 8.

consolidation hypothesis (kon-SOL-ih-DAY-shun high-POTH-uh-sis): The process by which new memories are transformed into long-term **memory** traces. Memories may be stored in the same areas of the brain that support active moment-to-moment functions like perception and speech control. Consolidation may involve synaptic changes in such brain regions, which make active neuronal connections more efficient. See Chapter 2, 'Consolidation of Short-Term Events into Long-Term Memory'.

contralateral (KON-tra-LAT-er-el; Latin for 'against the side'): The opposite side of the body or brain. See Chapter 2, 'Action'. See **ipsilateral**.

coronal (keh-RONE-el; from Latin *corona* = crown): A crown-shaped vertical slice of the brain that divides it into **anterior** and **posterior** halves. See Chapter 1, 'Some Starting Points'.

corpus callosum (KOR-pus kal-OS-um; from Latin *corpus* = body; Latin *callosum* = tough): A massive fiber bridge between the right and left hemispheres, consisting of more than 100 neuronal axons. It appears white when cut, because the axons are covered by white **myelin** cells. See Chapter 1, 'Some Starting Points'.

cortex (KOR-teks): See **cerebral cortex**.

cortical color blindness (KOR-ti-kel KUH-ler BLIND-ness): An inability to identify colors caused by damage to color-sensitive regions of the visual cortex. See Chapter 6, 'Brain Areas Necessary for Visual Awareness: Lesion Studies'.

cortical column (KOR-ti-kel KAW-lum; from Greek *cort* = skin, husk; Latin *columna* = top): A barrel-shaped slice of the six surface layers of **cortex** that often contain closely related **neurons**. Columns are about 0.5 mm in diameter and 2.5 mm in depth. They may be clustered into **hypercolumns**, which may be part of even larger clusters. See Chapter 5, 'Introduction'.

creole (KRAY-ole): A true language that children spontaneously evolve in multilingual communities. Creoles often are encountered in island communities where language communities overlap. 'Creoles' are contrasted with 'pidgins', which are dialects typically spoken by adults as a second language. Creoles are remarkable because they exhibit a full-fledged grammar, unlike pidgins. The spontaneity with which they arise suggests that human infants and children may be equipped with a biological language capacity with universal features. See Chapter 11, 'The Nature of Language' and Box 11.2.

Darwin, Charles (1809–1882): English naturalist who was among the first in modern times to make a persuasive case that all living species emerged from common ancestors over very long stretches of time, by 'survival of the fittest' and the most reproductively successful. Darwin also published important observations about emotional expressions in humans and animals. See Chapter 1, 'Some History, and Ongoing Debates'.

declarative memory (deh-KLAR-a-tiv MEM-ree; from Latin *declarare* = to make visible): The capacity to recall facts and beliefs. A kind of **explicit memory**. See Chapter 2, 'Classical Working Memory'.

déjà vu (DAY-zha VOO; French for 'already seen'): A feeling that one has lived through the present moment before. See Chapter 9, 'Varieties of Memory' and Box 9.3.

delta waves (DEL-tuh WAYVZ; fourth letter of Greek alphabet): A band of slow, high-amplitude electromagnetic waveforms associated with deep sleep, and recorded in the brain or on the scalp, apparently reflecting large populations of neurons. Delta generally is considered to be less than 2.5 Hz. It coexists with waking EEG as well, but becomes visible in the raw (unprocessed) EEG only when delta predominates in sleep and drowsy states. See Chapter 4, 'A Range of Useful Tools'.

dendrite (DEN-drite; from Greek *dendron* = tree): One of numerous thin, branched micron-level tubes extending from the cell body of a **neuron**. Dendrites typically receive synaptic stimulation from other neurons, and therefore serve as the input branches of the neuron. See Chapter 3, 'Introduction'.

Descartes, René (1596–1650): A French philosopher, mathematician, scientist, and writer who spent most of his adult life in the Dutch Republic. Descartes has been dubbed the 'Father of Modern Philosophy' and was also a careful student of the brain. He often is considered the originator of modern mind/body philosophy. See Chapter 1, 'Some History, and Ongoing Debates'.

developmental cognitive neuroscience (deh-vel-op-MEN-tel COG-ni-tiv NUR-o-si-ens): The study of the normal growth of the brain and its mental capacities. See Chapter 15, 'Introduction'.

diencephalons (die-en-SEF-a-lon; from Greek *dia-* = through; *enkephalos* = brain): The part of the brain that contains the **thalamus**, **hypothalamus**, and the posterior half of the **pituitary gland**.

diffusion tractography (di-FYOO-zhen trak-TOH-greh-fee; from Latin *diffusus* = scatter; *trahere* = to pull; Greek *graphein* = writing): A brain imaging technique that tracks the diffusion of water molecules in order to trace the major neuronal pathways of the brain. See Chapter 4 and the Appendix.

discourse (DIS-kors): A style of language usage in a community, often taken to reflect a particular political slant. See Chapter 11, 'Introduction'.

domain specificity (do-MANE spes-i-FIS-ih-tee): Functional specificity of brain regions or mechanisms. The idea that each cognitive function may have its own region or network of brain regions, rather than general-purpose brain mechanisms with multiple cognitive functions. See Chapter 12, 'A Closer Look at Frontal Lobe Function'.

dopamine (DOH-puh-meen): A major neuromodulator and neurotransmitter that is produced in several different parts of the brain, including the substantia nigra and ventral tegmental area. Dopamine has numerous functions, including voluntary movement control, reward, and inhibition of lactation (milk production) in females, sleep, mood, attention, and learning.

dorsal (DOR-sel; from *dorsum* = back): The upper part of a brain structure, also called **superior**.

dorsolateral syndrome (dor-so-LAT-er-el SIN-drome; from Latin *dorsum* = back; *latus* = side; *frons* = forehead): Deficits caused by damage to the **dorsolateral prefrontal cortex**, such as 'flat affect' (lack of emotion) and an impaired ability to switch to and initiate new actions. See Chapter 12, 'Frontal Lobe Dysfunction'.

dorsolateral prefrontal cortex (DOR-so-LAT-er-el pree-FRON-tal KOR-teks; from Latin *dorsum* = back; *latus* = side; *pre* = in front of; *frons* = the forehead; Greek *cortex* = bark): Prefrontal region involved in motor planning, executive control, self-regulation, emotion, and **working memory**. See Chapter 2, 'The Central Executive'.

dynamic causal modeling (die-NAM-ic KOS-el MO-del-ing; from Greek *dynamikos* = powerful; Latin *causa* = cause; Latin *modulus* = small measure): A method for interpreting brain data, such as *functional* **magnetic resonance imaging** (fMRI), that helps to interpret causal relationships among brain activities during a specified task. See Chapter 4, 'Correlation and Causation'.

echolalia (eh-ko-LAY-lee-eh; Greek *ēchō* = to repeat; *laliá* = babbling): Constant and uncontrollable imitation of the speech of others. Echolalia may be seen in autism, Tourette syndrome, **aphasia**, developmental disability, schizophrenia, Asperger syndrome, Alzheimer's disease, and other conditions. See Chapter 12, 'Frontal Lobe Dysfunction'.

echopraxia (eh-ko-PRAK-see-eh; from Greek *ēchō* = to repeat; *praxis* = action): A neurological symptom involving repeated, involuntary imitation of the movements of another person. See Chapter 12, 'Frontal Lobe Dysfunction'.

Edelman, Gerald M. (b. 1929). American immunologist and neurobiologist who won the Nobel Prize for his work on the structure of antibody molecules. Edelman developed the theoretical framework of Neural Darwinism, which applies Darwinian selectionist principles to the brain, in contrast to the instructionist principles of conventional computers. See Chapter 3 and Chapter 16.

electroencephalography (**EEG**; eh-LEK-tro-en-sef-eh-LOG-reh-fee; from Greek *ēlektron* = sunlight; *en-* + *kephalē* = in the head; *graphein* = writing): Electrical activity that typically is recorded on the scalp and sometimes on the surface of the **cortex**, reflecting the electromagnetic field of large numbers of active neurons. See Chapter 4, 'A Range of Useful Tools', and the appendix.

empathy (EM-path-ee; from Greek *empatheia* = passion): The capability to share one's feelings and understand another person's. See Chapter 14, 'Overview'.

enzyme (EN-zime; Greek, *en-* + *zyme* = yeast): Molecules that facilitate the rate of chemical reactions.

epigenesis (ep-ih-GEN-eh-sis; from Greek *epi* = after; Greek *genesis* = birth, origin): Non-DNA factors that shape cells during gestation (pregnancy) and after birth. Constrasted with the classical Central Dogma of molecular biology, in which DNA is recoded into transfer RNA, which ends in the production of proteins for the structure and functions of all cells. Epigenesis implies a flow of causality in the opposite direction. For example, numerous physiological and environmental factors can influence whether specific genes (DNA) are expressed or not. DNA is the primary molecule that encodes phenotypes, passing the plan for a species from one generation to the next. But non-DNA factors can influence the activation and silencing of DNA, the on/off switches. See Chapters 15 and 16.

epigenetics (ep-ih-juh-NET-iks; Greek *epi-* = after; *genesis* = birth, origin): Changes in gene expression caused by other mechanisms than the direct expression of DNA via messenger RNA and their resulting proteins. See Chapters 15 and 16.

episodic memory (ep-i-SOD-ic MEM-ree; from Greek *episeidos* = coming in besides): **Memory** for conscious experiences, especially those that can be explicitly recalled, such as times, places, events, associated emotions, and other contextual knowledge. The formation of new episodic memories requires the **medial temporal lobe**, especially the **hippocampal region** in combination with the **cerebral cortex**. See Chapters 2 and 9.

evoked potential (**EP**; ee-VOKD puh-TEN-shul; from Latin *evocare* = to call forth; *potentia* = power): Also called *event-related potential* (ERP). A quite stereotypical electrical voltage pattern obtained from the brain, after averaging a time-locked voltage to a stimulus or other known event. Traditionally, the **EP** was obtained by averaging the stimulus-locked **EEG** over numerous trials. Though the exact brain sources of **EPs** are still debated, they are highly sensitive to cognitive and emotional variables. See Chapter 4, 'A Range of Useful Tools'.

excitotoxicity (ek-SEYE-toh-tok-SIS-ih-tee; Latin, *excitare* = to arouse; *toxicum* = poison). Neural damaged caused by an excess of glutamate, the usually excitatory neurotransmitter. Excitotoxicity is believed to be a major cause of brain degeneration and post-injury damage. See Chapter 16.

executive attention (ek-ZEK-u-tiv a-TEN-shun): Also called **voluntary, goal-directed**, or **top-down attention**. The act of voluntarily focusing on one stream of conscious events while ignoring others. Also see **selective attention, stimulus-driven attention**. See Chapter 8.

executive function (ek-ZEK-u-tiv FUNK-shun): Also called **executive control** or **frontal lobe function**. Capacities such as

planning, cognitive flexibility, voluntary action, abstract thinking, rule acquisition, initiating correct actions and inhibiting incorrect ones, impulse control, and emotional regulation. See Chapter 12, 'Introduction'.

explicit memory (eks-PLI-sit MEM-ree; from Latin *explicitus* = clear): A type of **memory** involving conscious, intentional recollection of stored experiences, and knowledge. See **implicit memory**, **implicit learning**. See Chapter 2, 'Classical Working Memory', and Chapter 9, 'Introduction'.

extinction (eks-TINK-shun): The process by which learned behaviors cease to be reinforced and therefore decline in frequency. In **parietal neglect**, after damage to the right parietal lobe, the ability of stimuli presented to the left side of the visual field to cancel those presented to the right side. See Chapter 13, 'The Fear System'.

Fechner, Gustav (1801–1887): German physicist, mathematician, and pioneer in psychophysics. Fechner claimed to have solved the mind-body controversy when he demonstrated a general logarithmic relationship between subjective sensory intensity and physical stimulus intensity across many different sensory modalities. See Chapter 1, 'Some History, and Ongoing Debates'.

feedback (FEED-bak): 1. In goal-guided systems, a signal from the environment indicating the degree of error in achieving the goal. 2. In neuroscience and psychology, an environmental signal reflecting some neuronal event. This kind of neurofeedback often allows people to learn to control otherwise spontaneous neuronal activities. 3. In neural networks, a flow of information returning an output signal to the input layer of the network. Some theorists make a strong distinction between **feedback** and **re-entrant** signaling in the **thalamo-cortical** system of the brain. See **Neural Darwinism**. Chapters 3 and 6, 'Theories of Visual Consciousness: Where Does It Happen?'.

feedforward (feed-FOR-werd): 1. Signal passing from a simpler to a more complex stage of processing. 2. In sensorimotor guidance, preparing an internal action trajectory to obtain more precise feedback when the action is executed. This strategy is used in fast movement control in birds and humans, and even in machines like aerodynamically unstable jet planes. 3. In neural networks, passing information from earlier to later layers of the network.

fetal alcohol syndrome (FEE-tel AL-ko-hol SIN-drum): (**FAS**). Brain damage in a fetus due to the mother's alcohol consumption, a major health risk. See Chapter 15, 'Prenatal Development: From Blastocyst to Baby'.

first-person perspective (FERST PER-son per-SPEK-tiv): The conscious viewpoint of the self or 'I'. See Chapter 14, 'Overview'.

flanker task (FLANK-er TASK): A tool for studying visual attention, in which the subject is asked to respond as quickly as possible to a target at the center of gaze, or one located off-center by a known distance. The target is flanked by distracting stimuli, such as arrows or letters. The flanker task permits quantitative assessment of the subject's speed and accuracy in shifting attention to an expected or unexpected position of the target. Moving attention in an unexpected direction is taken to require **executive attention**, since it must override the prepared, expected shift. Flanker tasks generally require subjects to avoid voluntary eye movements, so that any change in accuracy or speed in response to a target can be attributed to **implicit** shifts of attention. See Chapter 8.

flash suppression (FLASH suh-PRESH-en): A variant of the binocular rivalry task, in which an image presented to one eye is suppressed by a flashed image to the other eye. See Chapter 8.

Fourier analysis (FOOR-ee-ay uh-NAL-a-sis): Named after French mathematician and physicist Joseph Fourier, who showed that any complex function can be decomposed into a finite set of sine and cosine functions. In music, for example, this implies that any complex sound can be decomposed into a set of pure tones (sine waves). Fourier analysis is routinely applied to decompose EEG and other complex brain signals into frequency bands. See Chapter 4, 'A Range of Useful Tools'.

Fragile X syndrome: A genetic disorder with a range of physical, cognitive, emotional, and behavioral deficits. The most common cause of mental retardation. See Chapter 16.

Freud, Sigmund (1856–1939): Austrian physician and neurologist who founded the psychoanalytic school of psychology, and a highly influential cultural figure. Freud is best known for his theories of the unconscious mind and for creating the clinical practice of psychoanalysis. He was also an early neurological researcher who developed an early neural network model and discovered a new chemical stain – gold chloride – which allowed certain brainstem neurons to stand out clearly under the microscope. Although many of Freud's ideas have fallen from favor, some brain phenomena, like the role of the frontal lobes in regulating emotional impulses and goal-conflicts, are broadly consistent with his point of view. See Chapter 1, 'Some History, and Ongoing Debates'.

frontal lobe (FRON-tal lobe): An large region of cortex located at the front of each cerebral hemisphere and positioned forward of the **parietal lobes** and above and in front of the **temporal lobes**. The executive functions of the frontal lobes include the ability to anticipate the consequences of actions, to plan and make decisions, to speak, to override inappropriate impulses and resolve conflicting goals, to understand the mental states of others, and to hold information in working memory. See Chapter 1, 'Some History, and Ongoing Debates', and Chapter 5, 'Introduction'.

functional fixedness (FUNK-shun-el FIKS-ed-ness): A cognitive set that tends to block a person from novel ways of acting, perceiving, or solving problems. See Chapter 10, 'Explicit Problem-Solving'.

functional magnetic resonance imaging (**fMRI**; FUNK-shun-el mag-NET-ic REZ-nence IH-ma-jing): A type of

specialized **magnetic resonance imaging (MRI)** that measures local blood oxygenation related to **neural** activity in specific parts of the brain. fMRI helped to make cognitive neuroscience possible. See Chapter 4, 'Introduction', 'fMRI and PET: Indirect Signals for Neural Activity'.

functional redundancy (FUNK-shun-el ree-DUN-den-see): Built-in backup functions in a system to prevent the complete failure of critical functions. For example, mammals have two lungs so that if one fails, the organism still has one lung to breathe. The brain has multiple redundant capabilities. See Chapter 3, 'Functional Redundancy'.

fusiform face area (FFA; FYOO-ze-form; from Latin *fusus* = spindle, after its shape): A specialized region in the **medial temporal lobe** that responds selectively to visual faces compared to other objects. See Chapter 6, 'Functional Organization of the Visual System'.

Gage, Phineas (1823–1860): A historic brain damage patient, whose railroad accident demonstrated remarkable spared cognitive capacities in spite of severe damage to the frontal lobes. Gage was a railroad foreman who had a two-foot-long thin tamping iron shot through the upper orbit of the left eye and out through the medial scalp, when an unstable dynamite charge exploded unexpectedly. Although Gage appeared to have no loss of perception, motor control, or speech, his personality changed in ways that have come to typify frontal lobe damage, especially a major loss of impulse control and long-term motivation. See Chapters 2 and 12.

gamma-aminobutyric acid (**GABA**; GAM-uh uh-mee-no-byoo-TEER-ic ASS-id): The major inhibitory **neurotransmitter** in the central nervous system. It plays an important role in regulating neuronal and behavioral excitability, including sleep. GABA is needed for brain oscillations and for the regulation of muscle tone. See Chapter 16.

gamma waves (GAM-a WAYVZ; third letter of Greek alphabet): A band of fast, low-amplitude electromagnetic waveforms associated with wakefulness and active thinking, and recorded in the brain or on the scalp, apparently reflecting the activities of large populations of neurons. The gamma band is thought to be centered near 40 Hz, ranging from 25 to 60 Hz. However, higher frequency waves are sometimes labeled gamma as well. Gamma is thought to reflect regional connectivity in the service of current tasks. See Chapter 4, 'A Range of Useful Tools'.

ganglion (GAN-glee-on; Latin for swelling): A large cluster of **neurons**. The major subcortical organs may be considered to be ganglia, such as the **basal ganglia**. They are often very large structures, and have multiple functions. They are typically composed of subdivisions, which themselves are often layered and folded arrays of nerve cells. See Chapter 5, 'From 'Where' to 'What': The Functional Roles of Brain Regions'.

gap junction (also called electrical synapse): A direct membrane-to-membrane junction between two neurons or glial cells. Gap junctions once were thought to be rare, but now are believed to exist throughout the brain, especially in **GABA**-ergic connections in the top layer of cortex.

genome (JEE-nome; Greek, *genea* = generation, race): The full genetic blueprint specifies a biological species. See Chapter 16.

genotype (JEE-no-tipe): A genome, often contrasted with the *phenotype* for a given species, which is the physiological expression of the genetic code. See Chapter 16.

gestalt (gesh-TALT; German for *form*): 1. A perceptual stimulus that cannot be reduced to simple subcomponents. 2. A branch of psychology based on the German concept of *Gestalt*, often summed up with the slogan that 'The whole is more than the sum of its parts'. Gestalt psychology has profoundly influenced the study of perception. See Chapter 6, 'Introduction'.

glial cell (GLEE-el SEL; from Greek *glia* = glue): Non-neuronal cells in the brain that support neurons, maintain neurochemical homeostasis, form protective **myelin sheath** around neurons, and process information. See Chapter 15, 'Prenatal Development: From Blastocyst to Baby'.

glutamate (**Glu**; GLOO-teh-mayt; from Latin *gluten* = glue): A molecule related to glutamic acid that is the most abundant excitatory **neurotransmitter** in the brain. See g**amma-aminobutyric acid** (**GABA**). See Chapters 3 and 16.

gray matter: The outer layers of the **cerebral cortex**, as seen with the naked eye. Gray matter contains the cell bodies of tens of billions of **neurons** that send white-covered **axons** in many directions below the cortical mantle. See **white matter**. See Chapter 5, 'Introduction'.

head-related transfer function (**HRTF**; HED reh-LAY-ted TRANS-fer FUNC-shun): A method for computing the location of sounds in auditory space. See Chapter 7, 'Functional Mapping of Auditory Processing'.

Hebbian learning (HEB-ee-en LUR-ning): According to Donald O. Hebb, 'neurons that fire together, wire together'. That is, two neurons strengthen their **synaptic** links if they are active at the same moment. This process forms **cell assemblies**. Introduced by Donald Hebb in 1949, it is also called Hebb's rule. See Chapter 3, 'How Neural Arrays Adapt and Learn'.

Helmoltz, Hermann von (1821–1894): German physician, physicist, and sensory scientist. His works on vision and audition are still read, but his best-known contribution was demonstrating the physical law of conservation of energy using electrical stimulation of dissected frog legs. Helmholtz was one of the first to propose that the visual system makes 'unconscious inferences' that go beyond the raw light input to the eyes, a controversial idea in his time that has become widely accepted. See Chapter 1, 'Some History, and Ongoing Debates'.

hemispheric lateralization (hem-is-FEER-ik lat-er-al-ih-ZAY-shun; from Greek *hēmi-* (half) + *sphairion* = sphere; and Latin *lateralis* = side): The degree to which certain brain functions are performed primarily by one *cerebral* hemisphere, the most prominent being speech production on the left side for most people. See Chapters 5, 9, and 11.

hemodynamics (HEE-mo-dye-NAM-ics; from *hema* = blood; *dynamos* = force): The study of blood flow changes, particularly in the brain, as an index of local neural activity. See Chapters 1 and 4.

hippocampus (hip-o-KAM-pes; Greek seahorse, from *hippos* = horse, *kampos* = sea monster): In the human brain, the hippocampi are looped structures in each of the two **medial temporal lobes**. The hippocampi are part of the **limbic system** and play basic roles in encoding and retrieving **episodic** and **semantic memories** and in spatial navigation. See Chapter 2, 'Classical Working Memory'.

histogenesis (HIS-to-gen-eh-sis; from Greek *histos* = mast, loom, beam, web; Greek *gignesthai* = to be born): The formation of specific cells from less differentiated progenitor cells. See Chapter 15, 'Prenatal Development: From Blastocyst to Baby'.

homeobox (**Hox**) (HO-mee-oh-boks; Greek *homos* = same): DNA segments that regulate body plans in animals and plants. Hox genes typically regulate other genes to have their effects.

homunculus (ho-MUN-cue-lus; Latin = little man): The distorted human body maps in the **primary somatosensory cortex** (the sensory homunculus) and in the **primary motor cortex** (the motor homunculus). The lips, hands, feet, and sex organs have more sensory neurons than other parts of the body, so the homunculus has correspondingly distorted large lips, hands, feet, and genitals. Each hemisphere contains a sensory and motor homunculus of the opposite side of the body. These body maps were discovered by neurosurgeon Wilder Penfield at the University of Montreal in the 1950s and 1960s. See Chapter 5, 'From 'Where' to 'What': The Functional Roles of Brain Regions'.

hydranencephaly (hi-dran-en-SEF-uh-lee; Greek, *hydr-* = water; *enkephalon* = in the head): A fetal disorder involving severe damage to the brain, including failure of the cortex to develop normally; the missing tissue is replaced by the watery cerebrospinal fluid. Hydrancephaly is more severe than hydrocephalus, in which brain development is more complete, though there is a build-up of cerebrospinal fluid in the ventricles. See Chapter 16.

hypercolumn (HEYE-per CAW-lum; from Greek *hyper* = above; Latin *columna* = top): A cluster of **columns** of **cortex** that often contain closely related **neurons**. See Chapter 5, 'Introduction'.

hypothalamus (hie-po-THAL-a-mus; from Latin *hypo* = below; Greek *thalamos* = chamber): The major neuroendocrine organ of each side the brain, with vital roles in the regulation of blood nutrients, motivation, appetite control, and other major life functions. The hypothalamus is located below each **thalamus** just above the **brainstem**. It is closely related to the **pituitary** and **pineal glands**. See Chapter 5, 'Growing a Brain from the Bottom Up'.

immediate memory (ih-MEE-dee-et MEM-er-ee): Also called short-term **memory**. The ability to recall something for 10 to 30 seconds without rehearsal. **Working memory** and **sensory memories** can be seen as specific kinds of immediate memory. See Chapter 2, 'Classical Working Memory'.

implicit memory (im-PLI-sit MEM-er-ee; from Latin *implicitus* = obscure): Unconscious **memory**, which may arise from conscious or unconscious events. See Chapter 2, 'Classical Working Memory', Chapter 9, 'Introduction'.

inattentional blindness (in-uh-TEN-shun-el BLIND-ness): A reliable experimental phenomenon in which one is not able to see things that are normally clearly visible. See Chapter 8.

inference (IN-fer-ens): Drawing a conclusion based on knowledge rather than direct observation. See Chapter 1, 'Some Starting Points'.

inferior (in-FEER-ee-er; from Latin *inferus* = lower): Below.

inhibitory control (in-HIB-ih-tor-ee; from Latin *in-* = not; Latin *habēre* = to have, to consider): Nerve impulses that act to damp down or stop a particular activity or response. See Chapter 12.

insula (IN-soo-la; Latin for island): A structure that is hidden in and underneath the **lateral sulcus**, covered up by the **temporal** and **parietal lobes**, and therefore appears as an island when the covering tissues are gently pulled away. The insula is involved in 'gut feelings', such as the sense of nausea and disgust, and possibly in emotional feelings and cravings. See Chapter 5, 'From 'Where' to 'What': The Functional Roles of Brain Regions'.

intentionality (in-ten-shen-AL-ih-tee): The 'aboutness' of mental events, their ability to represent aspects of the world. Distinguished from *intention* as a mental goal. See Chapter 14, 'Overview'.

interaural level difference (in-ter-OR-el; from Latin *inter-* = between; *auris* = ear): A method of sound localization in which the brain detects the small difference in loudness between the two ears that occurs when a sound travels toward the head from an angle. See Chapter 7, 'Functional Mapping of Auditory Processing'.

interaural-time-difference (in-ter-OR-el): A method of **sound localization** in which the brain detects the split-second delay between the time when sound from a lateral source reaches the near ear and when it reaches the far ear. See Chapter 7, 'Functional Mapping of Auditory Processing'.

intersubjectivity (IN-ter-sub-jek-TIV-ih-tee): The sharing of subjective experiences, such as infants' ability to point to and name a toy and receive validation from an adult. A crucial aspect of social cognition and language learning. See Chapter 14, 'Overview'.

intonation contour (in-toh-NAY-shun kon-TOOR): The 'melody' or sing-song of normal speech. In English and other languages, questions typically are given a different intonation contour compared with affirmative statements. See Chapter 11, 'The Sounds of Spoken Language'.

ionotropic receptor (eye-ono-TROP-ik ree-SEP-ter; Greek, *ion* = going; *tropos* = direction): A group of membrane receptor channels for charged particles like Ca+2, Cl-2, and Na+2. Ionotropic receptors may be opened or closed by **neurotransmitters**. Also called ligand-gated ion channels, or channel-linked receptors.

ipsilateral (IP-si-LAT-er-al; from Latin *ipse* = self; *latus* = side): On the same side of the body. See **contralateral**. See Chapter 2, 'Action'.

James, William (1842–1910): American psychologist and philosopher. James summarized the 19th century's studies of the human mind and brain. His **Briefer Psychology** (1893) was widely used as an introductory text in psychology well into the 1920s. James also influenced Western stream of consciousness literature, educational psychology, and the study of religious experience and mysticism. In philosophy he is considered a major exponent of pragmatism, and was a source for European phenomenology. He was the brother of novelist Henry James and of diarist Alice James. See Chapter 1, 'Some History, and Ongoing Debates'.

lateral (LAT-er-al; from Latin *lateralis* = side): On the side(s) of the brain. See Chapter 1, 'Some Starting Points'.

lateral geniculate nucleus (**LGN**; LAT-er-el jen-IK-yoo-let NOO-klee-us; from Latin *latus* = side; *genu* = knee-shaped; Latin *nux* = nut): A nucleus consisting of 'knee-shaped' layers of cells in the thalamus. It is the primary relay center between the **retina** of the eye and the **primary visual cortex** (Area V1). See Chapter 6, 'Functional Organization of the Visual System'.

lateral inhibition (LAT-er-el in-hi-BI-shun; from Latin *latus* = side; Latin *inhibitus* = restrain): The capacity of a **neuron** to reduce the activity of its neighboring cells in the same layer of neurons. See Chapter 3, 'Working Assumptions'.

lateral occipital complex (**LOC**; LAT-er-el ox-SIP-it-al KOM-pleks; from Latin *latus* = side; Latin *occiput* = rearmost part of the skull): A region on the side of the **occipital lobe** that has a general role in visual object recognition. See Chapter 6, 'Functional Organization of the Visual System'.

lateral sulcus (LAT-er-al SUL-cus; from Latin *latus* = side; *sulcus* = groove): Also called Sylvian fissure or lateral fissure. This prominent 'valley' divides the **temporal lobe** from the **frontal** and **parietal lobes**. See Chapter 1, 'Some Starting Points'.

L-dopa (el-DOH-puh; L = levorotatory, the leftward turning molecule; dopa = dihydroxyphenylalanine): The first medical dopamine agonist used to help Parkinson's patients by stimulating the production of dopamine in the substantia nigra. L-dopa is a natural precursor molecule in the synthesis of dopamine.

lexical identification (LEKS-ih-kul eye-den-tih-fih-KAY-shun; from Greek *lexis* = word): The process of assigning words to speech sounds. See Chapter 11, 'Introduction'.

lexicon (LEKS-ih-con; from Greek *lexis* = word): The vocabulary of a language. See Chapter 11, 'Introduction'.

limbic system (LIM-bik sis-tem; from Latin *limbus* = border): An ancient set of brain structures involved in emotion, memory, olfaction, and action control, including the **hippocampus**, **amygdala**, **thalamus**, **hypothalamus**, and **cingulate gyrus**. The limbic system is interwoven with the endocrine system and **autonomic nervous system**. See Chapter 13, 'Introduction'.

long-term depression (**LTD;** LONG TERM de-PRE-shun; from Latin *deprimere* = to press down): A lasting decrease in the strength of a **synapse**. Along with **long-term potentiation** (**LTP**), **LTD** is thought to be a synaptic basis for **learning** and long-term **memory**. See Chapter 3, 'How Neural Arrays Adapt and Learn'.

long-term potentiation (**LTP**; LONG TERM puh-ten-shee-AY-shun; from Latin *potentia* = power): A long-lasting strengthening of a synaptic link. Along with **LTD, LTP** is thought to be the synaptic basis of **learning** and long-term **memory**. See Chapter 3, 'How Neural Arrays Adapt and Learn'.

longitudinal fissure (lon-gi-TOOD-in-al FISH-er; from Latin *fissus* = crack, opening): The deep valley that divides the right and left hemispheres of the vertebrate brain. See Chapter 1, 'Some Starting Points'.

magnetic resonance imaging (**MRI**; mag-NET-ik REZ-nence IH-ma-jing; Latin *resonare* = to sound; *imago* = imitation): Based on the spin resonance of atomic nuclei, MRI is a technique used to visualize the internal structures of the body, including the brain. **Functional MRI** (**fMRI**) records brain activity and is often superimposed on the structural brain image obtained via **MRI**. See Chapter 4, 'Introduction'.

magnetoencephalography (**MEG**; mag-NET-o-en-sef-eh-LOG-gra-fee; Greek *en-* + *kephalē* = in the head; *graphein* = writing): An imaging technique based on the magnetic fields produced by brain activity. MEG is silent and noninvasive and has good temporal and spatial resolution. See Chapter 4, 'A Range of Useful Tools', and the appendix.

medial (MEE-dee-al): Toward the midline of the body. **midsagittal**. See Chapter 1, 'Some Starting Points'.

medial temporal lobe (**MTL**; MEE-dee-el TEM-per-el LOBE): The bottom aspect of the **temporal** lobes, which are arranged symmetrically around the midline, and contain evolutionarily ancient olfactory structures, memory encoding and recall, and emotional functions. See Chapter 5, 'From 'Where' to 'What': The Functional Roles of Brain Regions'.

memory (MEM-ree, MEM-eh-ree; from Latin *memor* = mindful): A lasting brain representation that is reflected in thinking, experience, or behavior. See Chapter 9.

mental flexibility (MEN-tel fleks-ih-BIL-ih-tee; from Latin *mens* = mind; Latin *flexus* = bent; Latin *-ibilis*, from *-bilis* = capable or worthy of): Also called ability to shift **cognitive set**. The capacity to respond rapidly to unanticipated environmental contingencies. See Chapter 12, 'A Closer Look at Frontal Lobe Function'.

mental rigidity (MEN-tel rih-GID-ih-tee; from Latin *mens* = mind; Latin *rigidus* = stiff): The inability to respond rapidly to unanticipated environmental contingencies, or shift **cognitive set**. Profound forms of mental rigidity produce obsessive-compulsive disorder. **Frontal lobe** damage often produces extreme mental rigidity. See Chapter 12, 'Frontal Lobe Dysfunction'.

mentalize (MEN-tel-ize; from Latin *mens* = mind): The ability to understand the self and others, not just as sensory objects but also as subjective beings with mental states. See Chapter 14, 'Overview'.

metabotropic receptor (meh-tab-oh-TROP-ik ree-SEP-ter; Greek, *metabole* = change; *tropos* = direction). Neuronal receptors that make use of the existing metabolic machinery of the cell to activate post-synaptic signaling. Contrasted with ionotropic receptors, which utilized ion channels in the cell membrane.

metacognition (MET-a-cog-NI-shen; from Greek *meta* = above; Latin *cognere* = to know): Knowing about cognition. Self-knowledge about memory, perception, or voluntary control. See Chapter 8.

midsagittal (mid-SAJ-i-tal; from Latin *sagitta* = arrow): **medial**. The midline plane of section, going from the nose to the middle of the back of the head. See Chapter 1, 'Some Starting Points'.

mind (from Greek *menos* = spirit): Those aspects of intellect and **consciousness** manifested in thought, perception, **memory,** emotion, will, and imagination, including all of the brain's conscious and unconscious cognitive processes. See Chapter 1, 'Some History, and Ongoing Debates'.

mind-reading (from Greek *menos* = spirit): The attempt to attune one's own actions to the minds of others. Most people are not accurate mind-readers in most circumstances. See Chapter 14, 'Overview'.

mirror neuron (MEER-er NUR-on or NYOO-ron; from Greek *neuron* = sinew, nerve): A neuron theorized to fire both when an animal performs an action and when it observes the same action performed by another. Large populations of mirror neurons have been found in primates and are believed to exist in other species, including birds. In humans, brain activity consistent with mirror neurons has been found in the premotor **cortex** and the **inferior parietal cortex**, however there is significant debate in the field regarding these findings. See Chapter 14.

mirror neuron system (MEER-er NUR-on or NYOO-ron SIS-tem; from Greek *neuron* = sinew, nerve): The presumed network of **mirror neurons** in the human brain, which is believed to be needed for social cognition. See Chapter 14.

mitochondrion (MEYE-toh-KON-dree-on; Greek *mitos* = thread, *chondrion* = grain): Plural, mitochondria. The energy-producing organelle in most animal cells. Mitochondria are believed to originate in blue-green algae that migrated into animal cells and established a mutual dependence or symbiosis. Mitochondria are the chief source of the energy molecule ATP (adenosine triphosphate), and are indispensible for life in animals. They have their own nuclei with DNA, but much of their DNA has migrated to the nucleus of the host cell. Because energy production is a fundamental life process, the metabolic machinery of mitochondria has also been recruited for other functions like neuronal signaling. See Chapter 16.

module theory (MAH-jul THEE-eh-ree or THIR-ee; from Latin *modulus* = little measure; Greek *theōria* = contemplation): A type of theory that postulates that different brain functions may be localized in different regions or networks of the brain. See Chapter 14, 'Overview'.

morpheme (MOR-feem; from Greek *morphē* = form): The smallest linguistic unit that can convey meaningful information by itself. In English, prefixes and suffixes are considered to be morphemes (e.g., 'pre-' and 'post-'). See Chapter 11, 'Introduction'.

motion blindness (MO-shun BLIND-nes): A symptom caused by injury to brain regions needed for motion perception, such as **area MT** of the visual cortex, resulting in an inability to perceive visual motion. See Chapter 6, 'Brain Areas Necessary for Visual Awareness: Lesion Studies'.

multistable perception (MUL-tee-STAY-bel per-SEP-shun): Alternating visual perceptions of an ambiguous stimulus. See Chapter 6, 'Linking Brain Activity and Visual Experience'.

myelin (MY-e-lin; from Latin *myel* = marrow): A sheath of glial cells, called the myelin sheath, surrounding the **axons** of many **neurons**. Myelinated axons appear **white**, hence the '**white matter**' of the visible brain. See Chapters 1 and 3.

near infrared spectroscopy (**NIRS**; NEER in-fra-RED spek-TROS-kop-ee; from Latin *infra* = below, within; Greek *erythros* = red): A method of measuring light waves below the color red in the wavelength spectrum (about 800 nm to 2500 nm). It is used to measure blood hemoglobin as an index of regional brain activity. See Chapter 15, 'Developing Mind and Brain'.

neglect (nuh-GLEKT): A type of brain damage to the right parietal lobe, in which the patient fails to consciously perceive or attend to the left side of objects or scenes. See Chapter 6, 'Brain Areas Necessary for Visual Awareness: Lesion Studies'.

neocortex (NEE-o-COR-tex; from Latin *neo* = new; Greek *cort* = bark): The largest and most visible part of the human cerebral cortex. It is the 'new' cortex from an evolutionary point of view, as contrasted with the 'old' cortex of the **medial temporal lobe**, **hippocampus**, and olfactory brain. See Chapter 1, 'Some History, and Ongoing Debates'.

neon color spreading (NEE-on CAW-ler SPRED-ing): A perceptual illusion in which white space appears to be tinted by proximity to colored and black lines. See Chapter 6, 'Linking Brain Activity and Visual Experience'.

Neural Darwinism (NUR-el DAR-win-izm; from Greek *neuron* = nerve): A theory proposed by neuroscientist Gerald

Edelman that suggests that neurons develop and make connections following Darwinian principles. In biological evolution, species adapt by reproduction, mutations leading to diverse forms, and selection among the resulting repertoire of slightly different organisms. Neural Darwinism suggests that brains develop in similar fashion, both in the reproduction, variation, and selection of developing neurons, and in a later stage, in the Darwinian selection of synaptic connections. Brains are said to be *selectionist* rather than *instructionist*, unlike the program of a digital computer. See Chapter 3, 'How Neural Arrays Adapt and Learn'.

neural migration (NUR-el my-GRAY-shun; from Greek *neuron* = nerve): Movement of nerve cells from their place of origin toward their final location in the growing brain. See Chapter 15, 'Prenatal Development: From Blastocyst to Baby'.

neural net model (NUR-el NET MO-del; from Greek *neuron* = nerve): Also known as **artificial neural nets (ANNs)**, neural models are simulated, simplified models of selected brain functions. Most are relatively small in scale and do not represent the great complexity of the brain. However, they are important for a better understanding of how neural computation might work. See Chapter 3.

neural tube (NOOR-el TOOB): In developing vertebrate embryos, the cylindrical structure that will turn into the **central nervous system**. See Chapter 15, 'Prenatal Development: From Blastocyst to Baby'.

neuroblast (NUR-o-blast; from Greek *neuron* = nerve; Greek *blastos* = bud, shoot): In early embryos, a dividing cell that will differentiate into **neurons** or **glial cells**. See Chapter 15, 'Prenatal Development: From Blastocyst to Baby'.

neurogenesis (NOOR-oh-JEN-uh-sis; Greek *neuron* = nerve cells; *genesis* = beginning): The origin and differentiation of neurons from progenitor cells. See Chapter 15, 'Prenatal Development: From Blastocyst to Baby'.

neuromodulator (NOOR-o-MOD-u-lay-ter; from Greek *neuron* = nerve; *modulate* is used in the sense of 'influence' or 'regulate'): Certain neurochemicals have very widespread effects in large regions of the brain. These are called **neuromodulators**, whereas **neurotransmitters** are molecules with very local effects in specific synapses. See Chapters 1 and 16.

neuron (NOOR-on or NYOO-ron; from Greek *neuron* = nerve): Nerve cells that transmit information by electrochemical signaling. They are the core components of the human brain, spinal cord, and peripheral nerves. Many different types of neurons exist, from sensory receptors and motor units and neuroendocrine cells to pyramidal neurons, which have long-distance axons, interneurons, which form bushy local connections, and a wide variety of specialized cells. See Chapter 3.

neuron doctrine (NOOR-on or NYOO-ron DOK-trin; from Greek *neuron* = nerve; *doctor* = teacher): A theory credited to the Spanish histologist **Santiago Ramón y Cajal**, stating that 'the nervous system consists of numerous nerve units (**neurons**), anatomically and genetically independent'. This has been one of the basic assumptions of brain science for the past century. However, the discovery of large numbers of electrical synapses (gap junctions) may challenge some aspects of the neuron doctrine. See Chapter 1, 'Some History, and Ongoing Debates'.

neuropeptide (NOOR-o-PEP-tide; from Greek *neuron* = nerve; Latin *peptidia* = small digestibles): A peptide is a short amino acid chain. Neuropeptides act as local neurotransmitters or neurohormones, influencing appetite regulation, growth hormone, and pain perception. See Chapters 1 and 3.

neurotoxin (NOOR-oh-tok-sin; Greek, *neuron* = nerve cell; Latin, *toxicum* = poison): A chemical that degrades neural functioning, often by blocking normal neural signaling. See Chapter 16.

neurotransmission (NOOT-oh-trans-MISH-en):Electrochemical signaling between nerve cells. See Chapters 3 and 16.

neurotransmitter (NOOR-o-TRANS-mit-er; from Greek *neuron* = nerve; Latin *trans* = moving through): Chemicals that act to relay a signal from one neuron to the next across a synaptic cleft. Some neurotransmitters are packaged into **vesicles** that cluster beneath the membrane on the presynaptic side of a **synapse** and are released into the **synaptic cleft**, where they bind to receptors located on the postsynaptic membrane. Release of neurotransmitters often is driven by **action potentials** in the presynaptic axon. There is a low level of baseline release even in the absence of an action potential. See Chapters 1, 3, and 16.

neurulation (nur-uh-LAY-shun or nyur-uh-LAY-shun; from Greek *neuron* = nerve): The early development of the **central nervous system** in the vertebrate fetus. See Chapter 15, 'Prenatal Development: From Blastocyst to Baby'.

norepinephrine (nor-epih-NEF-rin; Greek, *epi* = on top of; *nephros* = kidney; *-in* = protein): Also called noradrenaline. A brain chemical with dual roles as a circulatory hormone and a chemical neurotransmitter. See **adrenaline, noradrenaline**. See Chapter 16.

object permanence (OB-jekt PER-ma-nens): The knowledge that perceptual objects continue to exist even when they cannot be seen or touched. Object permanence begins in infants around 7 months. See Chapter 15, 'Developing Mind and Brain'.

occipital lobe (ox-SIP-it-al lowb; from Latin *occiput* = a back bone of the skull): The occipital lobes, which contain the earliest visual region of the cortex, are the smallest of four lobes in the human **cerebral cortex**. See Chapters 1 and 5.

ontogeny (on-TODG-en-ee; from Greek *ontos* = being; Greek *geneia* = origin): The development or course of development, especially of an individual organism. See Chapter 12, 'Phylogeny and Ontogeny'.

orbitofrontal cortex (or-bit-oh-FRON-tel COR-teks; from Latin *orbis* = circle, orb, orbit, world, referring to the part of the brain immediately above the sockets or *orbits* of the two eyes; Greek *cortex* = bark): A specific frontal lobe syndrome where patients may show euphoria, hyperactivity, and loss of impulse control. See Chapter 12, 'Frontal Lobe Dysfunction'.

orbitofrontal syndrome (or-bit-oh-FRON-tel SIN-drome; from Latin *orbis* = circle, orb, orbit, world, referring to the **orbitofrontal cortex** immediately above the sockets or *orbits* of the two eyes): A specific frontal lobe syndrome where patients may show euphoria, hyperactivity, and loss of impulse control. See Chapter 12, 'Frontal Lobe Dysfunction'.

output functions (OWT-put FUNK-shuns): Brain processes controlled by the **frontal lobes** that include the **central executive**, action planning, and motor output. Chapter 2, 'Classical Working Memory'.

paleocortex (PAY-lee-o-COR-teks; from Greek *paleo* = old, ancient; Greek *cortex* = bark): An evolutionary ancient region of the **cerebral cortex** including the **medial temporal lobes**, olfactory cortex, and **hippocampus**. See Chapter 2, 'Classical Working Memory'.

Panksepp, Jaak (b. 1943): A founder of **affective neuroscience**, the study of the brain basis of emotion. Panksepp is known for his research on laughter in other mammals (in response to tickling) as well as high-frequency separation distress cries, such as occurs when rat mothers and their pups are separated. See Chapter 13, 'Panksepp's Emotional Brain Systems'.

parahippocampal place area (PAIR-a-HIP-o-KAMP-el; from Greek *para* = before; see **hippocampus (PPA)**): A region near the hippocampus that responds more strongly to landscapes and visual scenes than to isolated objects like houses or faces. See Chapter 6, 'Functional Organization of the Visual System'.

paralinguistic (PAIR-uh-lin-GWIS-tik; from Greek from *para* = near; Latin *lingua* = language): The nonverbal aspects of linguistic communication, such as voice intonation, gesture, social distance, and eye contact. See Chapter 11, 'Meaningful Statements'.

pathology (path-OL-uh-gee; from Greek *pathologia* = study of the emotions): Something abnormal. The study of the essential nature of diseases and especially of the structural and functional changes produced by them. See Chapter 12, 'Frontal Lobe Dysfunction'.

periaqueductal gray matter (**PAG**; peh-ree-ah-kwa-DUK-tel GRAY MA-ter; from Greek *peri* = near; Latin *aquaeductus* = water channel): The gray matter that surrounds the midbrain and **brainstem** tube (aqueduct) that carries cerebrospinal fluid between the ventricles and the spinal cord. See Chapter 13, 'The Fear System'.

parietal lobe (puh-REYE-uh-tl lowb; from Latin *parietalis* = relating to walls): A large cortical region located above the **occipital lobe** and behind the **frontal lobe**. The parietal lobe integrates sensory information from different modalities, and contains constantly updated maps of the position of the body and nearby objects. See Chapters 1 and 5.

parietal neglect (puh-REYE-uh-tl neh-GLEKT; from Latin *parietalis* = relating to walls): A condition in which damage to the right parietal lobe causes the left side of egocentric space to become unconscious. See Chapter 13, 'The Fear System'.

Pavlov, Ivan Petrovich (1849–1936): Russian physiologist. He was awarded the Nobel Prize in Physiology or Medicine in 1904 for research pertaining to the digestive system. He is best known for describing 'classical conditioning', in which an arbitrary stimulus like the sound of a bell came to signal the coming of a biological stimulus like food, thereby eliciting salivation. Pavlov's proposal that conditional reflexes are the basic unit of all human **learning** is no longer generally believed. However, Pavlovian conditioning is widely used in research and is relevant to clinical issues such as food preferences and aversions, and perhaps anxiety disorders. See Chapter 1, 'Some History, and Ongoing Debates'.

Penfield, Wilder (1891–1976): A neurosurgeon and researcher in Montreal who performed pioneering work in epileptic surgery. Before operating, he performed exploratory brain stimulation in awake patients (who were free of pain using only local anesthetic in the surgical opening). Thus patients could report their experiences upon electrical brain stimulation. Penfield and coworkers were able to determine functions of the human brain that were previously only approachable via postmortem studies of brain damaged patients. See Chapter 4, 'A Range of Useful Tools'.

perceptual filling in (per-SEP-choo-el FIL-ing in): A general feature of sensory perception in which the brain fills in missing parts of a visual object or scene, often far beyond the direct sensory input. See Chapter 6, 'Linking Brain Activity and Visual Experience'.

perceptual memory (per-SEP-choo-el MEM-ree, MEM-eh-ree; from Latin *memor* = mindful): Long-lasting changes in one's ability to perceive the world, e.g., the ability to perceive the sounds of speech, and to recognize visual objects under changes in orientation and lighting. See Chapter 2, 'Classical Working Memory'.

peripheral nervous system (**PNS**; per-IF-er-el NUHR-vus SIS-tem): The extensive network of neurons outside of the brain and spinal. The PNS includes sensorimotor neurons below the neck, and autonomic neurons that innervate the smooth musculature of the digestive tract, heart, and circulatory system. See Chapter 5, 'Introduction'.

perseveration (per-sev-er-AY-shun; from Latin *perseverare* = persist): A symptom involving the inappropriate and uncontrollable repetition of a specific word, phrase, or gesture. See Chapter 10, 'Explicit Problem-Solving'.

phenotype (FEE-no-tipe; Greek *phainein* = to show; *typos* = type): Any physiological trait of an organism that expresses the DNA blueprint, or genotype. See Chapter 16.

phoneme (FO-neem; from Greek *phōnē* = sound): In human languages, the smallest lexically distinctive category of sound, such as consonants and vowels. See Chapter 7, 'Speech Perception'.

phonemic deficit (fo-NEEM-ic; from Greek *phōnē* = sound): A form of **aphasia** in which speech sounds cannot be identified in terms of **phonemic** categories. See Chapter 7, 'Speech Perception'.

phosphene (FOS-feen; from Greek *phos* = light; Greek *phainein* = to show): Light spots in the visual field that are induced by direct mechanical, electrical, or other stimulation of the retina or visual cortex. Phosphenes have also been reported by meditators, during sensory isolation, and under the influence of drugs, such as hallucinogens. See Chapter 6, 'Manipulation of Visual Awareness'.

phylogeny (feye-LODG-en-ee; from Greek *phylon* = race; Greek *geneia* = origin): The evolutionary history of a kind of organism or a genetically related group of organisms, as distinguished from the development of the individual organism. See Chapter 12, 'Phylogeny and Ontogeny'.

pituitary gland (pi-TOO-uh-tehree gland; from Latin *pituita* = phlegm, from the former belief that the pituitary secreted phlegm): The 'master gland' of the body, also called the hypophysis. An endocrine gland about the size of a pea that appears to hang from the **hypothalamus** at the base of the brain. The pituitary works with the hypothalamus to regulate developmental stages and homeostasis. See Chapter 5, 'Growing a Brain from the Bottom Up'.

planum temporale (PLAH-num tem-por-AHL-eh; from Latin *planum* = a flat surface; Latin *temporalis* = of the temple): A part of the **auditory cortex** involved in sound analysis and particularly speech perception. See Chapter 7, 'Functional Mapping of Auditory Processing'.

plasticity (plas-TI-SI-tee; from Greek *plastikos*, from *plassein* = to mold, form): The ability of the brain to adapt and reorganize to new environmental inputs or demands, or following brain damage. See Chapter 7, 'Music Perception'.

pons (PONZ; Latin, *pons* = bridge): A prominent anterior bulge in the **brainstem**. The pons relays sensory information between the **cerebellum** and the forebrain and spinal cord, helps to control sleep and wakefulness, and regulates respiration among other functions. It also generates **REM sleep** signals that are interpreted by the cortex as visually vivid, narrative dreams. See Chapter 5, 'Growing a Brain from the Bottom Up'.

positron emission tomography (**PET**; POH-zi-tron ee-MISH-en tom-OG-reh-fee; Latin *emitterre* = to send out; Greek *tomos* = section; Greek *graphein* = writing): Positrons are positively charged subnuclear particles, typically produced by a particle accelerator. PET is a low-level radioactive imaging technique that allows the computational extraction of brain or body slice maps, from which a three-dimensional image can be constructed. See Chapter 4.

postcentral gyrus (post-SEN-tral JEYE-res; from Latin *post* = behind; Latin *gyrus* = ridge): A protruding fold in the **parietal lobe** of the human brain immediately behind the **central sulcus**. It includes the **primary somatosensory cortex**, the first cortical map of the body senses, also called the **sensory homunculus**, which represents the opposite or **contralateral** side of the body.

posterior (pos-TEER-ee-er; from Latin *post* = after): Behind. In brain anatomy, **posterior** is synonymous with **caudal**.

prefrontal cortex (pree-FRON-tal KOR-teks; from Latin *prae* = in front of; *frons* = the forehead; Greek *cort* = bark): The large, forward portion of the **frontal lobes**, not including the motor cortex. Prefrontal cortex includes **executive** functions and Broca's area, and is sometimes called 'the organ of civilization'. See Chapter 2, 'Classical Working Memory'.

primary motor cortex (PRIE-mar-ee MO-ter KOR-teks; from Latin *primus* = first; Greek *cort* = bark): The brain region that directly controls skeletal (voluntary) muscles. It corresponds to the **motor homunculus**, and works in close association with other sensory body and motor maps, such as the premotor cortex.

primary somatosensory cortex (PRIE-mar-ee so-MAT-o-SENS-ery KOR-tex; from Latin *primus* = first, most important; *soma* = body; *sensus* = sense; Greek *cort* = bark): The sensory homunculus (body map), located on the **postcentral gyrus** of the cortex, it is the first cortical area for the body senses.

primary visual cortex (PRIE-mar-ee VIZH-oo-el KOR-teks; from Latin *primus* = first, most important; Latin *visus* = sight; Greek *cort* = bark) (also called V1): The first cortical map of the visual system, located in the **occipital lobe**. See Chapter 6, 'Functional Organization of the Visual System'.

problem space (PROB-lem SPAYS): A graph of the decision points in problem solving, often in the form of a tree structure. See Chapter 10, 'Explicit Problem Solving'.

procedural memory (pruh-SEE-der-el MEM-ree, MEM-eh-ree; from Latin *procedere* = a way of doing things; Latin *memor* = mindful): A form of **implicit memory** equivalent to skill memory, or knowing how to do a task. It appears to be largely unconscious. This type of **memory** is often very durable. See Chapter 2, 'Classical Working Memory'.

process specificity (PRAH-ses spes-i-FIS-ih-tee): The claim that a cognitive process may utilize a variety of different brain regions. See Chapter 12, 'A Closer Look at Frontal Lobe Function'.

proprioception (PRO-pree-o-SEP-shun; from Latin *proprius* = one's own; Latin *perceptio* = perceiving): Senses relating to the

self, including one's location in space, based both on internal and external sensory input.

proteome (PRO-tee-OME; by analogy to genome): The entire set of proteins expressed by a genome.

pure word deafness: The inability to comprehend spoken word meanings, while still being able to hear sounds, to speak, read, and write. Associated with bilateral damage to the **posterior superior** (rear upper) **temporal lobes** or their subcortical connections. See Chapter 7, 'Speech Perception'.

radial unit model (RAY-dee-el YOO-nit MAH-del): A model of **neural migration** proposed by neuroscientist **Pasko Rakic** that asserts that in the developing cerebral cortex, the cells are created at the base of each cortical column and each new cell migrates past its predecessors. See Chapter 15, 'Prenatal Development: From Blastocyst to Baby'.

Rakic, Pasko (b. 1933) (rah-KEECH): A neuroanatomist who showed that neural migration occurs radially as well as rostrally, like the outflowing spokes of a forward-moving wheel. See Chapter 15, 'Prenatal Development: From Blastocyst to Baby'.

Ramón y Cajal, Santiago (1852–1934): Spanish pioneer in microscopic studies of the brain. He often is considered to be the founder of brain science. Many of his detailed drawings of brain tissue slices are still presented today. See Chapter 1, 'Some History, and Ongoing Debates'.

receptive field (ree-SEP-tiv FEELD; from Latin *recipere* = to take): The receptive field of a nerve cell in the visual system, for example, is the region of the visual field that can activate or inhibit the firing of the cell. The receptive field of a retinal receptor is therefore different from the receptive field of a higher level cell tuned to detect motion or visual object identity. Analogous receptive fields have been found for visual attention in the parietal lobe. Receptive fields are found in other sensory systems as well, such as the auditory and somatosensory systems. See Chapter 3, and Chapter 6 for more discussion on receptive fields in the visual system.

re-entrant connectivity (ree-EN-trent con-ec-TIV-e-tee): Most brain connections are bidirectional, in that activity at point A triggers activity at point B and vice versa. See Chapter 3, 'Working Assumptions'.

re-entry (ree-entry): In Neural Darwinism, the resonant looping between two neurons or arrays of neurons, so that neuron A activates neuron B and vice versa. Re-entry can also take place between neuronal populations. It is believed to be the primary signaling mechanism among brain regions, and therefore closely related to brain rhythms.

reflex circuit (REE-fleks SIR-kut): Also called a reflex arc, this is the relatively simple pathway that mediates a reflex action. The most common example is the knee-jerk (or patellar tendon) spinal reflex, which occurs even when the spinal cord is isolated from the brain. However, spinal reflexes can be quite fast, complex, and coordinated, and may interact with the brainstem and the vestibular (balance) system, as in the case of a cat reorienting its body during a fall. Normally reflexes work in close coordination with voluntary control via the frontal lobes, cerebellum, and basal ganglia. Cranial reflexes like the pupillary reflex are under the joint control of autonomic, visual, and emotional regions of the brain. See Chapter 3, 'Working Assumptions'.

region of interest (**ROI**; REE-gen of IN-trest): A region of the brain selected to be tested in a brain imaging study, in order to make statistically valid predictions about expected activity in that region. See Chapter 4.

replication (rep-lih-KAY-shun): 1. Copying of a genome in inheritance. 2. Redoing an experiment by using the exact same methods in order to verify the findings with a new subject group.

reticular formation (reh-TIC-u-ler for-MAY-shun; from Latin *reticulum* = network): A part of the brainstem that is involved in the sleep-waking cycle and many other functions. It receives collateral input from all sensory and motor systems, as well as from higher-level brain structures. It is evolutionarily one of the oldest parts of the brain. See Chapter 5, 'From 'Where' to 'What': The Functional Roles of Brain Regions'.

reticulofrontal disconnection syndrome (reh-tic-yoo-lo-FRON-tel dis-kon-EK-shun SIN-drome; from Latin *reticulum* = network; *frons* = the forehead): A deficit of executive functioning thought to be caused by damage to the pathways connecting the **frontal lobes** to the 'network-like' (reticular) structures of the **brainstem** and mesencephalon. See Chapter 12, 'Frontal Lobe Dysfunction'.

retina (REH-tin-a): The array of light receptors lining the inner surface of the eye. Light striking retinal receptors (rods or cones) trigger a chemical reaction that evokes a change in electrical potential across the cell membrane. This may trigger activity in retinal ganglion cells that project their axons to make up the optic nerve, which terminates in the visual relay nucleus of the thalamus. See Chapter 6, 'Functional Organization of the Visual System'.

retrograde amnesia (RET-ro-grayd am-NEE-zhuh; from from Latin *retrogradus* = going back; Greek *a-mnēsia* = without memory): A form of memory loss extending before the time of brain injury. Contrasted with **anterograde amnesia**. See Chapter 9, 'Amnesia'.

retrovirus (RET-roh-VEYE-rus; Latin, *retro* = backward; *virus* = venom). A virus that acts in reverse from the conventional flow of DNA-RNA-protein. Retroviruses are RNA parasites that can be integrated into the DNA of host cells. The HIV virus was the first retrovirus to be studied in great detail. Retroviruses are utilized to insert or delete specific genes into cellular DNA.

reversal conditioning (ree-VER-sel kon-DISH-un-ing): A technique using **classical conditioning** in which an animal is first conditioned to fear one stimulus and not to fear another one. In the next phase, these conditions are switched, and the animal must adapt to a rapid reversal of the cues for fearful events. See Chapter 13, 'The Fear System'.

sagittal (SAJ-i-tal; from Latin *sagitta* = arrow): Any section of the brain that runs parallel to the **medial** or **midline** cut. See Chapter 1, 'Some Starting Points'.

scotoma (skeh-TO-ma): A damaged or missing part of the retina, or of a higher-level neuronal map of the visual field. Scotomas often are filled in with information from regions adjacent to the missing neurons. See Chapter 6, 'Manipulation of Visual Awareness'.

second-person perspective (SEH-kond PER-son per-SPEK-tiv): A person-to-person point of view, considered as a meeting between two subjective perspectives, self and other. See Chapter 14, 'Overview'.

selectionism (suh-LEK-shun-izm): A brain theory based on Neural Darwinism. In biological evolution species adapt by reproduction, mutations leading to diverse forms, and selection among the resulting repertoire of slightly different organisms. Neural Darwinism suggests a similar selectionist process in the growth of neurons and their synaptic connections. See Chapter 3, 'How Neural Arrays Adapt and Learn'.

selective attention (suh-LEC-tiv a-TEN-shun): The ability to pay attention to one aspect of the environment while ignoring competing stimuli. This may occur voluntarily, as in choosing to read an interesting book while sitting on a noisy bus, or when one sensory experience is biologically or personally significant. See Chapters 2 and 8.

semantic deficit (seh-MAN-tic DEF-ih-sit): A form of **aphasia** involving a loss of a particular domain of meaning, such as animal names. See Chapter 7, 'Speech Perception'.

semantic memory (seh-MAN-tic MEM-ree or MEM-er-ee): A type of **declarative memory** that involves meanings, factual beliefs, categories, and other general knowledge going beyond specific experiences. See Chapter 2, 'Classical Working Memory'.

semantics (seh-MAN-tiks): The study of meaning in language. See Chapter 11, 'Introduction'.

sensory system (SEN-suh-ree SIS-tem): Part of the nervous system responsible for processing sensory information. A sensory system consists of sensory receptors, neural pathways, and mostly posterior cortex involved in sensory perception. The classical senses have many subsenses, like pain and even tickle sensations, light receptors in the eye that trigger melatonin as a sleep hormone, the balance sense, and the like. Not all sensory systems yield conscious experiences; blood pressure, for example, which is sensed by hypothalamic neurons, is rarely conscious. The classical senses begin with receptor surfaces containing many millions of receptors, such as the retina and the basilar membrane. See Chapter 2, 'Introduction'.

sequential grouping (seh-KWEN-shul GROOP-ing): One way in which the human auditory system organizes sound into perceptually meaningful elements. If sound properties are repeated in the same sequence, they may be grouped together. See Chapter 7, 'Functional Mapping of Auditory Processing'.

serotonin (seh-roh-TOE-nin; Latin, *serum* = blood, *tonus* = tension): A neurotransmitter that was originally discovered as a blood-pressure-regulating hormone. Serotonin has multiple functions in the brain and spinal cord, and serotonin dysfunction is believed to be responsible for some brain disorders.

shadowing (SHA-doe-ing): An experimental technique to study selective attention in which subjects repeat speech immediately after hearing it. With practice, subjects can learn to shadow speech with a lag time of less than a second. The shadowing task is sufficiently demanding that other streams of speech cannot be understood at the same time. See Chapter 8.

simulation theory (sim-yoo-LAY-shun THEE-eh-ree): The notion that we sometimes mentally simulate or imitate what we believe others to be experiencing, in order to understand them. See Chapter 14, 'Overview'.

simultaneous grouping (SEYE-mul-TAY-nee-us GROOP-ing): If two sounds have common onsets (beginnings) and offsets (endings), they may be grouped together. One way in which the human auditory system organizes sound into meaningful elements. See Chapter 7, 'Functional Mapping of Auditory Processing'.

sound localization (SOUND lo-cal-ih-ZAY-shun): Identifying the location of a sound, often based on **binaural disparities** of timing and loudness between the two ears. See Chapter 7, 'Functional Mapping of Auditory Processing'.

source memory (SORS MEM-ree or MEM-er-ee): **Memory** for the specific time, place, and circumstances when an event was experienced. See Chapter 9, 'Varieties of Memory'.

spectrograph (SPEK-tro-graf; from Latin *spectrum* = appearance; Greek *graphon* = to write): A machine developed during World War II by Bell Telephone Laboratories to analyze sound signals and produce a picture called a spectrogram, showing sound frequencies over time. See Chapter 7, 'Speech Perception'.

spiking code (SPI-king CODE): The rate and pattern of action potentials, which may transmit useful information in the brain. See Chapter 3, 'Arrays and Maps'.

stimulus-driven attention (STIM-u-lus DRI-vn a-TEN-shun): The capture of **attention** by salient stimuli. See Chapter 8.

Stroop test (STROOP test): Named after American psychologist John Ridley Stroop, who first wrote about this phenomenon in English in 1935. When the name of a color, such as *blue*, *green*, or *red*, is printed in a color differing from that expressed by the word's meaning (e.g., the word red is printed in blue ink), a subject has more difficulty naming the color of the word and is slower and more prone to errors than when the meaning of the word is congruent with its color.

This phenomenon is known as the Stroop effect. The Stroop effect is useful in activating conflict-related regions of the brain, and generalizes well to related tasks, like the 'emotional Stroop'. See Chapter 8.

superior (soo-PEER-ee-er): Above. In the human brain, it is synonymous with **dorsal**.

supratemporal plane (SOO-pra-tem-per-el PLANE): A flat region of **cortex** in the Sylvian fissure, where primary and secondary auditory cortex and parts of **Wernicke's area** are located. See Chapter 5, 'From 'Where' to 'What': the Functional Roles of Brain Regions'.

Sylvian fissure (SIL-vee-en FISH-er): Also called the **lateral sulcus** or lateral fissure. This prominent 'valley' of the cortex divides the **frontal lobe** and parietal lobe above from the **temporal lobe** below. See Chapter 5.

synapse (SIN-aps): Synapses are tiny gaps between neurons that communicate by way of chemical neurotransmitters. Synapses are a basic computational element of the brain, a kind of traffic control point for the flow of information. The brain has tens of billions of neurons, but it has many trillions of synapses.

synaptic cleft (sin-AP-tic CLEFT): The space between two **neurons** that can communicate with each other via neurotransmitters. See Chapter 3.

synaptic pruning (sin-AP-tik PROO-ning): The selective loss of **synapses** in the brain when some potential connections are not utilized. See **Hebbian learning, neural Darwinism**. See Chapter 15, 'The Developing Brain: A Lifetime of Change'.

synaptogenesis (sin-AP-toe-GEN-eh-sis): The birth of **synapses** in the brain. See Chapter 15, 'The Developing Brain: A Lifetime of Change'.

syntactic analysis (sin-TAK-tik uh-NAL-ih-sus): The identification of grammatical structures from words, phonemes, and morphemes. See Chapter 11, 'Introduction'.

syntax (sin-TAKS): The rules and regularities of sentences in natural languages. See Chapter 11, 'Introduction', and 'Syntax, Nesting, and Sequencing'.

Talairach coordinates (tal-AY-rahk co-ORE-din-etz): A precise three-dimensional coordinate system for the human brain that can localize any point in the brain with millimeter precision. See Chapter 5, 'Introduction'.

temporal envelope (TEM-por-al EN-ve-lope; from Latin *tempor* = time): The rising and falling intensity of speech signals over time. See Chapter 7, 'Speech Perception'.

temporal lobe (TEM-por-al lobe): The temporal lobes are parts of the cerebral **cortex** that are involved in visual perception, hearing and speech perception, and **memory encoding** and **recall**. They emerge from the sides of the cortex, beneath the **lateral sulcus**. In profile, if the human brain resembles a boxing glove, the temporal lobes would be the thumb of each side. The temporal lobe envelops the **hippocampus** and **amygdala** and is therefore involved in emotion and memory formation as well. The **medial temporal** lobe (most easily seen from the bottom perspective of the brain) is ancient paleocortex, including olfactory cortex. See Chapters 1 and 5.

teratogen (ter-AT-e-jen): A chemical or other factor that causes developmental malformations. See Chapter 15, 'Prenatal Development: From Blastocyst to Baby'.

terminal (TER-mi-nul): The distal end of an **axon**. See Chapter 3, 'Introduction'.

thalamo-cortical system (THAL-a-mo COR-ti-kel SIS-tem; from Greek *thalamos* = chamber; Greek *cort* = bark): A central hub in the brain involving the **cortex** and **thalamus**, allowing signal traffic to flow flexibly back and forth in both directions. See Chapter 5, 'Introduction'.

thalamus (THAL-a-mus; from Greek *thalamos* = room, chamber): A pair of symmetric egg-shaped structures in the brain that provide the main cortical input hub and cortico-cortical traffic hub. See Chapter 1, 'Some History, and Ongoing Debates'.

theory of mind (THEE-eh-ree or THIR-ee of MIND): The ability to attribute mental states – beliefs, desires, intentions – to others. See Chapter 14, 'Overview'.

theory (THEE-eh-ree or THIR-ee): The notion that children develop implicit theories of other people over time, much as scientists produce theories over many years of testing and development. See Chapter 14, 'Overview'.

theta waves (THAY-ta WAVZ; eighth letter of Greek alphabet): Theta waves are regular electromagnetic waveforms with a typical frequency of 3.5 to 7.5 Hz. One role of theta is to coordinate hippocampal memory encoding with the neocortical sites of synaptic memory storage. Theta is also involved with the reverse process of episodic retrieval. Theta rhythms are thought to involve many **neurons** firing in synchrony, driven by cholinergic neuromodulation.

third-person perspective (THIRD PER-son per-SPEK-tiv): A public viewpoint on evidence. Public evidence for some hypothesis is typically required in science. See Chapter 14, 'Overview'.

transcranial magnetic stimulation (**TMS**; trans-CRAY-nee-el mag-NET-ic stim-yoo-LAY-shun): A relatively noninvasive method using powerful electromagnets outside of the head to stimulate or inhibit cortical neurons. TMS shows good temporal and spatial resolution. See Chapter 4, 'A Range of Useful Tools'.

transcription (tran-SKRIP-shun; Latin *trans* = across, *scribere* = to write): The copying of DNA into messenger RNA. See Chapter 16.

translation (trans-LAY-shun): The conversion of messenger RNA into active proteins.

triune brain (TRY-oon BRAYN; Latin, *tri* = three): A broad model proposed by Paul MacLean to characterize the human brain in terms of three major evolutionary stages of

development, including the reptilian complex, limbic system (mammalian), and neocortex (primates and other large-brained mammals, with a large frontal lobe expansion in humans). See Chapter 13.

unconscious perception (un-CON-shus per-SEP-shun): Sensory stimulus processing without awareness of the stimulus. See Chapter 6, 'Manipulation of Visual Awareness'.

utilization behavior (yoo-til-ih-ZAY-shun be-HAYV-yor): Also called *field-dependent behavior*. A frontal lobe disorder in which victims may imitate the actions of an examining physician or find it irresistible to use tools placed in front of them. See Chapter 12, 'Frontal Lobe Dysfunction'.

ventral (VEN-trel; from Latin *venter* = the belly): The lower part of a brain structure, inferior.

ventricles (VEN-trik-lz): Four small cavities in the brain containing circulating cerebrospinal fluid. The ventricular walls have been found to be sites for neural stem cells. See Chapter 5, 'Growing a Brain from the Bottom Up'.

ventromedial prefrontal cortex (ven-tro-MEE-dee-el pree-FRON-tal KOR-teks; Latin *venter* = the belly; *medialis* = in the middle): The bottom midline structures of the frontal lobe, especially in humans and other primates. This region, extending backward from the top of the nose, is involved in emotions, infant-mother bonding, fear, and risk in decision making. See Chapter 12.

verbal dyspraxia (VER-bl dis-PRAK-see-uh; Greek, *dys-* = impaired; *praxis*, action): A condition in which speaking is impaired. See Chapter 16.

verbal rehearsal (VER-bel ree-HER-sel): Mental repetition of words to be remembered, using the 'inner speech' component of *working memory*. Inner speech involves a spontaneous commentary on current concerns, goals, and emotions. See Chapter 2, 'Classical Working Memory'.

Vesalius, Andreas (1514–1564): Belgian physician who produced the first accurate atlas of human anatomy in 1543, called **On the Fabric of the Human Body**. Vesalius' book was a major milestone in the Renaissance rediscovery of science and medicine. See Chapter 1, 'Some History, and Ongoing Debates'.

vesicle (VES-i-cl; from Latin *vesicula* = small bladder): The small bubbles filled with of neurotransmitter molecules that travel through the axon to the synaptic terminals, where they fuse with the synaptic membrane to release neuromolecules into the cleft when an action potential occurs. Neurotransmitters then diffuse across the synapse to trigger depolarization of the postsynaptic membrane, ultimately leading to another axonal spike. Vesicles are essential for the propagation of signals between neurons and are constantly recreated by the cell. See Chapters 3 and 16.

visual agnosia (VI-zhoo-el ag-NO-zhe; from Greek *agnōsia* = lacking knowledge): A condition in which a person has difficulty recognizing objects because of damage to object-recognition regions of the cortex, such as the inferior temporal lobe. See Chapter 6, 'Brain Areas Necessary for Visual Awareness: Lesion Studies'.

visual backward masking (VI-zhoo-el BAK-werd MAS-king): A conscious visual image can be 'erased' by a subsequent visual event, such as a cross-hatch display, even though the conscious event is not physically blocked from reaching the retina. See Chapter 8.

visual phantoms (VIZH-oo-el FAN-tems; from Anglo-French *fantasme* = phantasm): A form of **perceptual filling in** in which visual forms seem to float in front of the surrounding shapes and colors that create the illusion. See Chapter 6, 'Linking Brain Activity and Visual Experience'.

visuospatial sketchpad (vizh-oo-oh-SPAY-shul SKECH-pad): The ability to hold visual and spatial information momentarily in **working memory**. See Chapter 2, 'Classical Working Memory'.

vocoder (VO-CO-der; from *voice* + *coder*): A technology developed by Bell Telephone Laboratories to transmit highly filtered speech with minimum loss of intelligibility. The technology forms the basis for cochlear implants. See Chapter 7, 'Speech Perception' and Box 7.1.

volition (vuh-LI-shun): Voluntary control of actions, as contrasted with automatic control, as in the case of highly practiced habits. Many brain disorders involve a loss of voluntary control. See Chapter 12.

Wearing, Clive (b. 1938): A prominent British classical musician who suffered a viral brain infection in his forties that destroyed both hippocampi and some frontal lobe regions. Wearing's case has become well known due to the efforts of his wife, Deborah Wearing, to raise public awareness of such medical conditions. Wearing lives in a single, blindered moment, without the ability to store information for later recall. Despite his **memory** problems, he is still able to play the piano and conduct musical pieces he knew well before the brain injury. See **anterograde amnesia**. See Chapter 2, 'Classical Working Memory'.

Wernicke, Carl (1848–1905): German physician and discoverer of a selective cortical region for speech comprehension. This region is now referred to as **Wernicke's area**, and the associated deficit is known as **Wernicke's** or **receptive aphasia**. Patients with this deficit cannot understand speech, including their own, but produce fluent-sounding (but not usually meaningful) speech. See Chapter 1, 'Some History, and Ongoing Debates'.

Wernicke's aphasia (WER-nik-ees AY-PHAY-zha; from *a* = without; Latin *phasia* = utterance): See **Wernicke, Carl**. See Chapter 1, 'Some History, and Ongoing Debates'; Chapter 7, 'Speech Perception'.

Wernicke's area (WER-nik-ees AIR-ee-a): An area of the upper posterior temporal lobe that is needed for language comprehension. See Chapter 1, 'Some History, and Ongoing Debates'.

white matter: In the brain white matter consists of dense bundles of myelinated **axons**, which connect various **gray matter** areas of the brain to each other. White matter is named for the appearance or massive numbers of **myelinated** nerve axons, which appear to form the visible core of brain structure. See Chapter 1, 'Some History, and Ongoing Debates'.

working memory (WUR-king MEM-ree or MEM-er-ee): A cognitive capacity for storing and manipulating novel information over 10 to 30 seconds. Working memory includes **central executive, working storage, verbal rehearsal**, and the **visuospatial sketchpad**. See Chapter 2, 'Classical Working Memory'.

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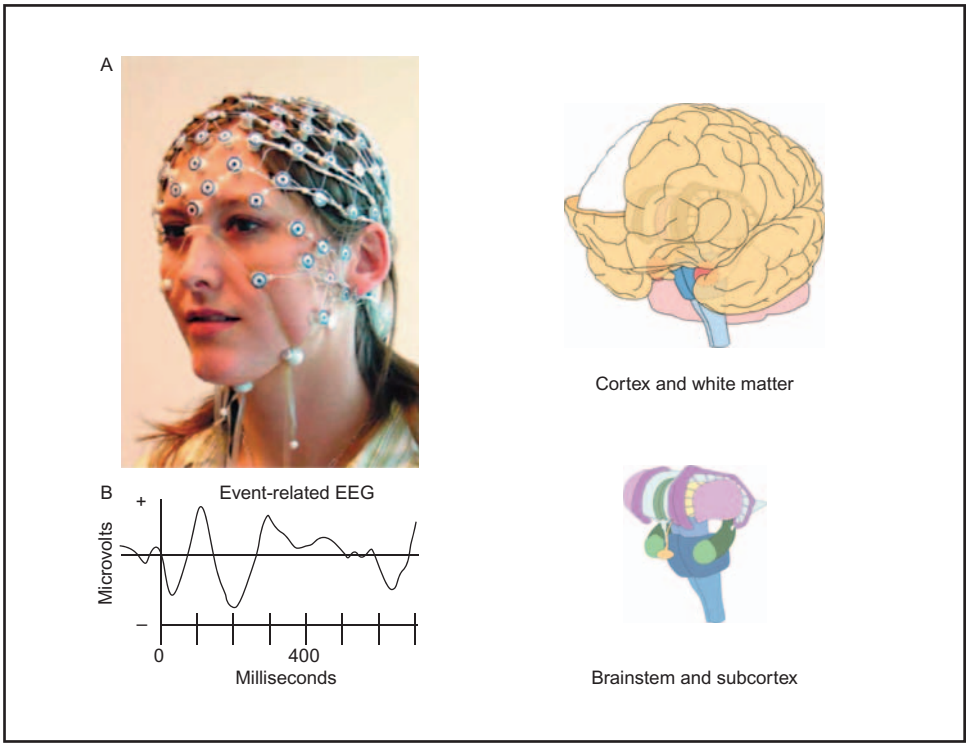

PLATE 1 A first approach to the anatomy of the brain. A. Always keep in mind how the brain is situated in the human head. It's the first step in appreciating the spatial layout of the cortex, which is filled with some 85% white matter, the shielded 'highways' that link all the major regions to each other. *Bottom right*: The cortex is mounted on the brainstem and subcortex, which flows up from the spinal cord. The event-related EEG is a reminder that the young lady in A has a constant, dynamic flow of massive signal traffic flowing through her brain, which we can pick up with surface EEG.

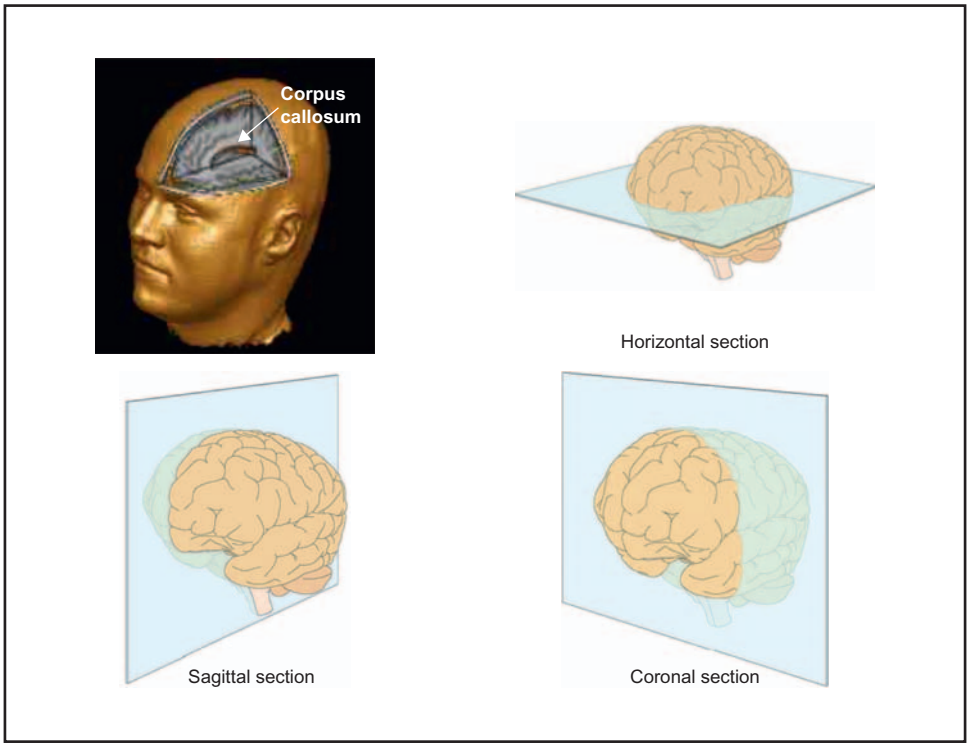

PLATE 2 Use the human head (upper left) to stay oriented. We can see the corpus callosum from the left side. The brain has three major planes of section to keep in mind.

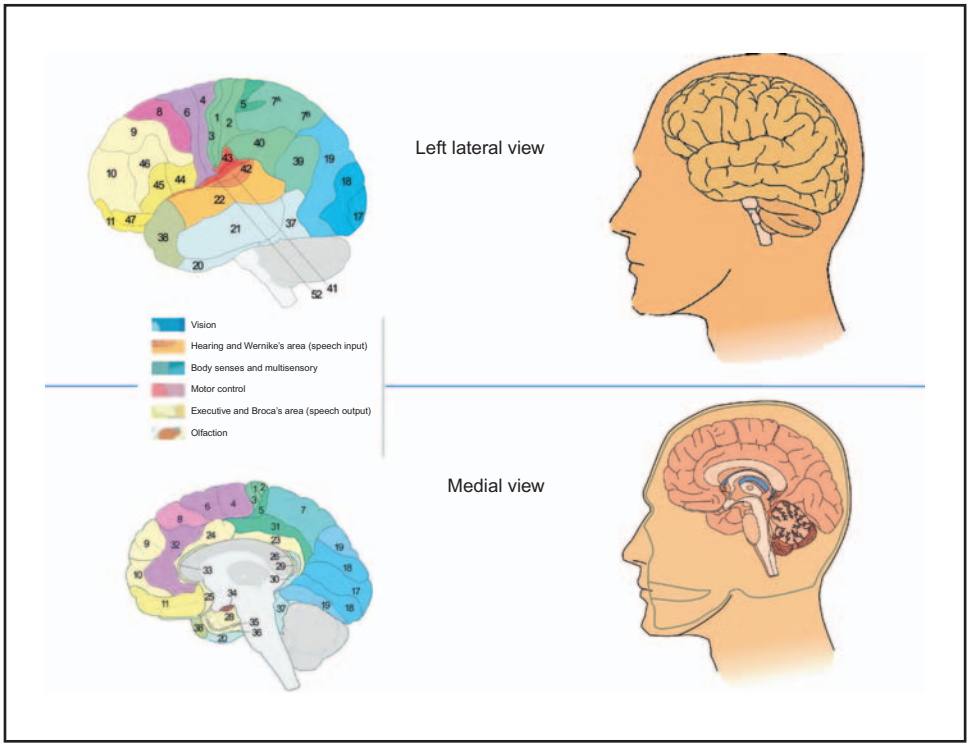

PLATE 3 The specialized regions of the cortex, the huge covering of the brain. Cortex is a flat sheet that is folded into the upper cranium. Notice the colored regions – the major functions of the cortex. It is the cortex that is believed to support the specific contents of conscious experiences. Its posterior half is sensory, its front half is motor and 'future directed' – cognition, working memory, planning, decision-making.

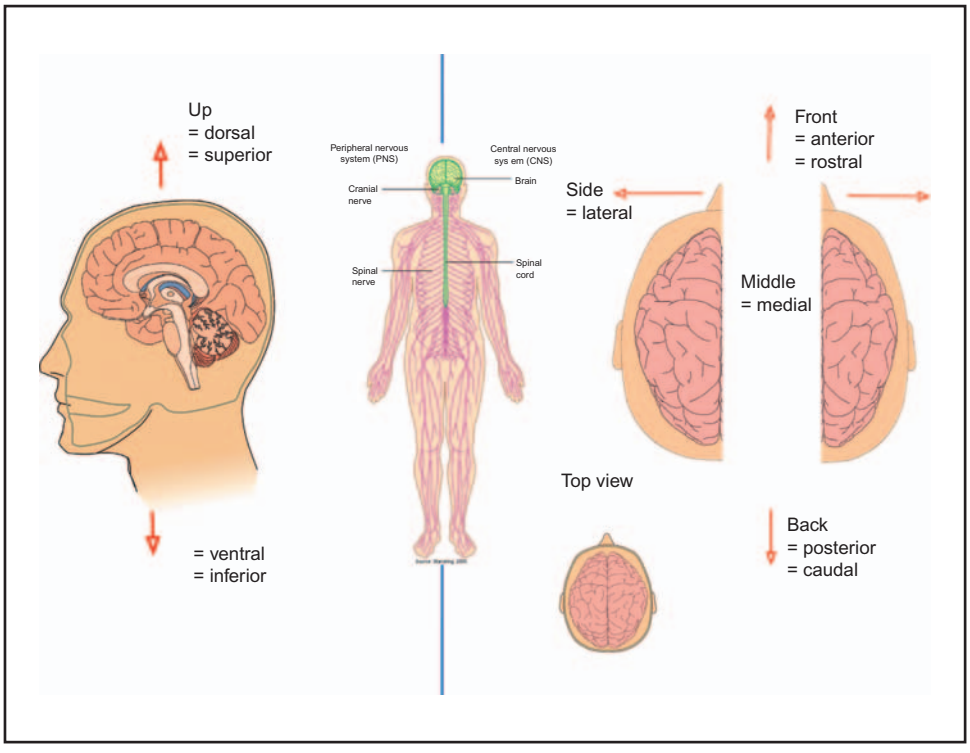

PLATE 4 Neurons pervade the body, and the spinal cord is a great highway channel between the brain and the rest of the body. Left, we see the brain from a left medial perspective. Notice the canonical directions, which are like North, South, East and West in geography. The simplest terms are given on top (Up, Down, etc.). But anatomists always use the Latin-based words. Use this figure for reference if you need to understand a brain figure in the book.

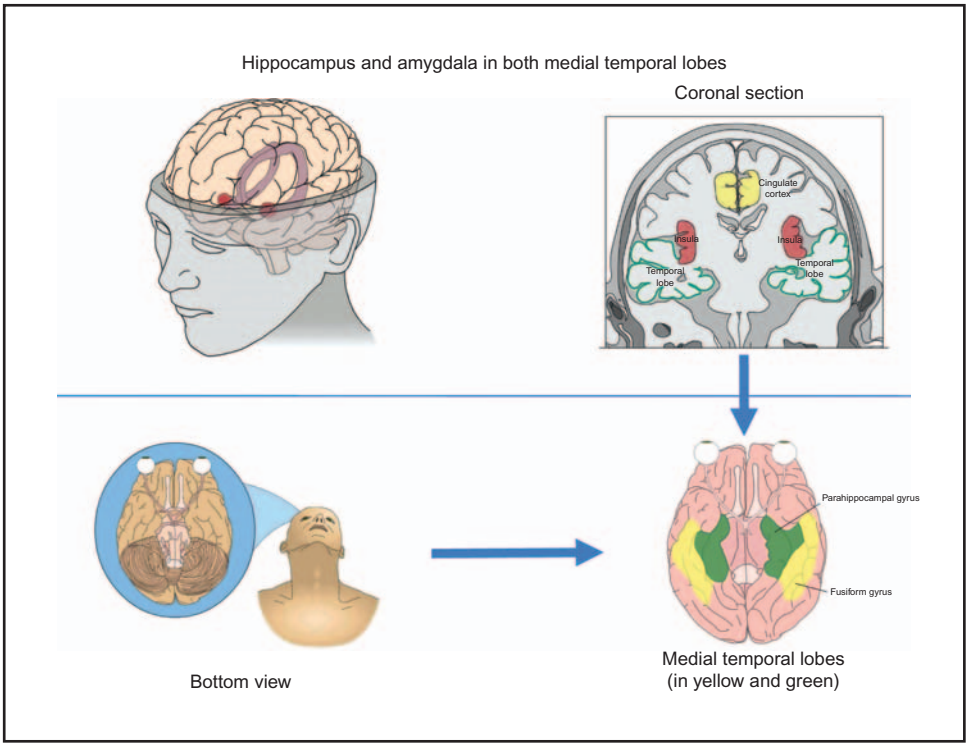

PLATE 5 Again, begin with the human head, and notice how the two hippocampi are nestled inside of each of the two temporal lobes. A vertical slice from ear to ear (coronal) only shows the hippocampi as small circular disks (red). On the bottom, if you imagine craning the head backward, you can visualize the location of the medial temporal lobe (MTL) which contains the two hippocampi. Those structures are crucial for emotion, vision, and memory.

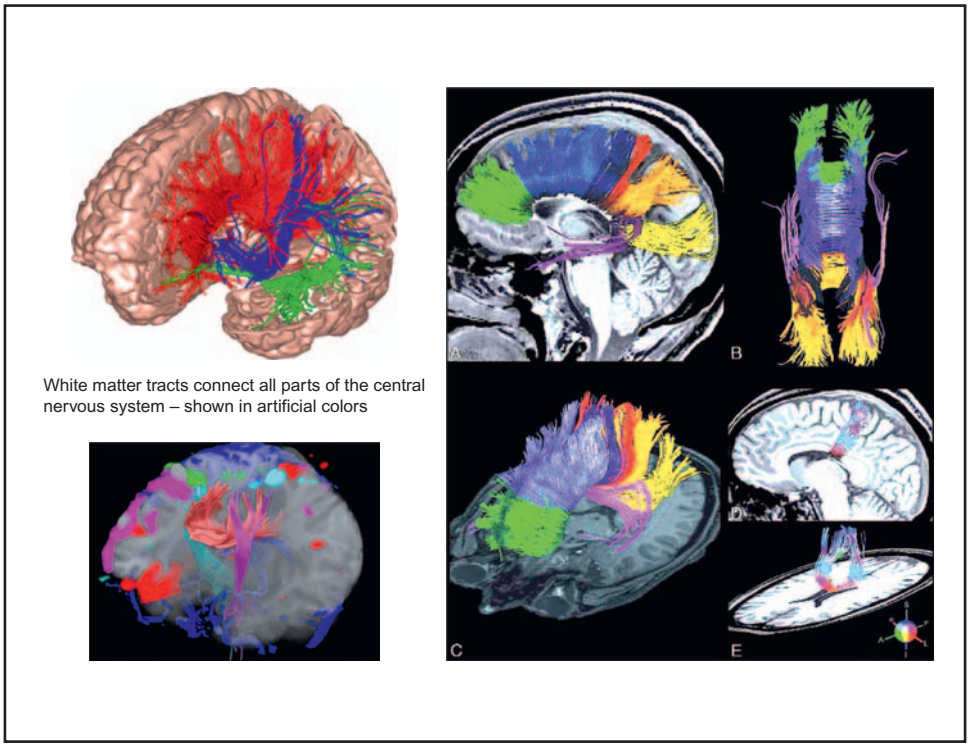

PLATE 6 *Upper Left*: The white matter tracts emerge in a great 'fountain' of fiber tracts from the thalamus. Other fiber tracts run in all the major directions. Below and to the right are *tractographs*, specialized MRI scans that show the massive highways between all major parts of the brain. Almost all are bi-directional. *Source*: Upper left, Izhikevich & Edelman, 2008; right side: Hofer & Frahm, 2006.

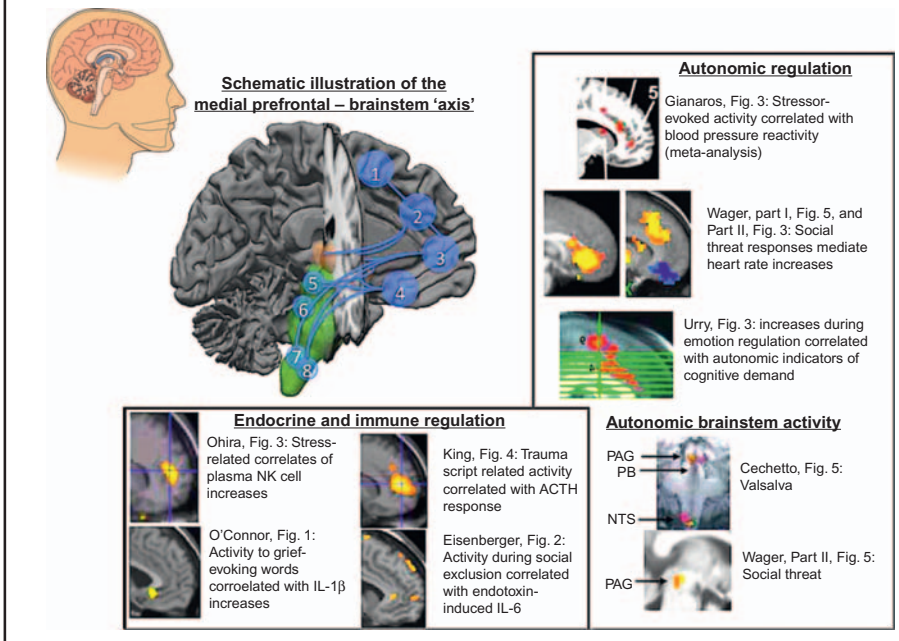

PLATE 7 The body and brain are highly interconnected. Upper left, we see how the medial view of the brain (facing right) is well-connected with endocrine system (hormonal) and immune regulation, and with autonomic regulation (heart, lungs, stomach, intestines, and blood vessels). Humans have no voluntary control over these functions, unlike our external muscles of the body and head. *Source*: Lane & Wager, 2009.

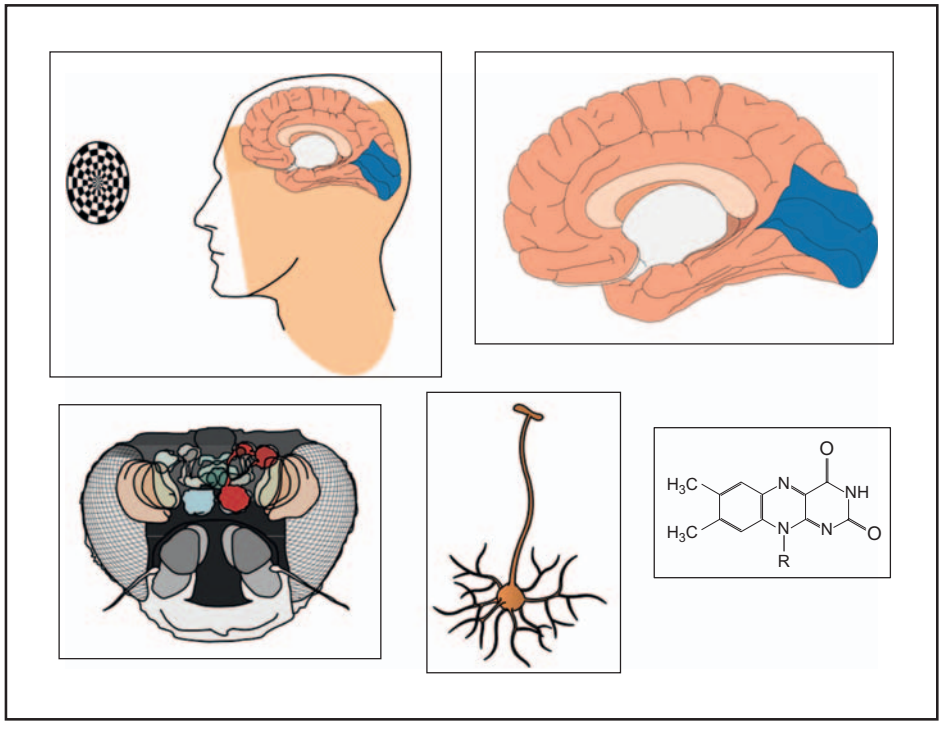

PLATE 8 A wider perspective. On the upper left, we see a person looking at a rotating visual disk, which triggers widespread brain activity, beginning in area V1 (dark blue). V1 is as big as a credit card, but it is folded inside the occipital lobe. Below, we see a comparison to a fruit fly brain, which has perhaps 100 000 neurons. A single neuron is shown to the right, followed by a single organic molecule, an amino acid (because of the amine fraction (NH), and a carboxyl fraction (COOH). All the vertices in the diagram stand for carbon atoms. R refers to a side chain, which could be quite variable. All levels of analysis, from molecules to gross anatomy, are vitally important. All proteins and many neurotransmitters involve amino acids.