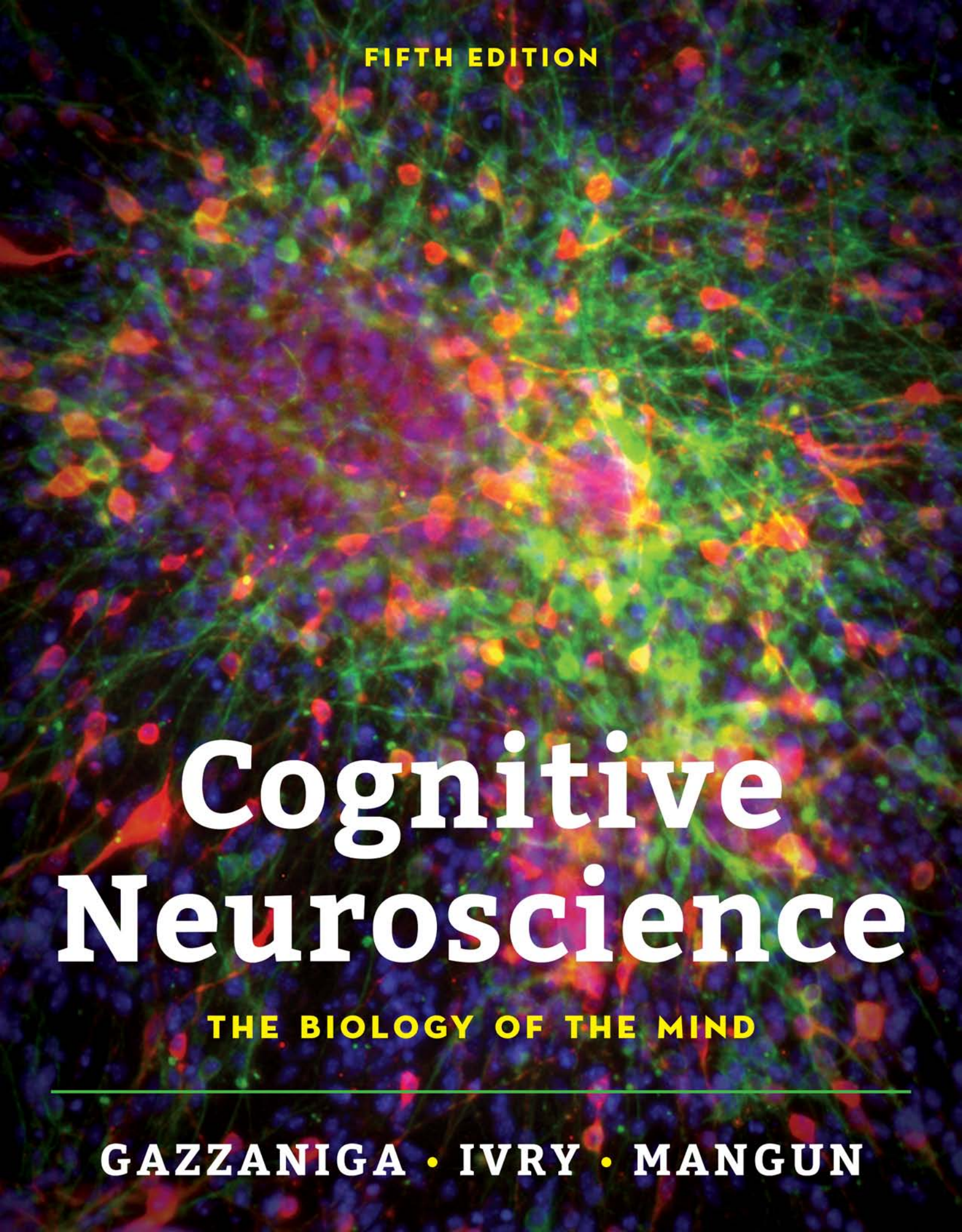

FIFTH EDITION
Cognitive Neuroscience
THE BIOLOGY OF THE MIND
GAZZANIGA • IVRY • MANGUN

FIFTH EDITION

Cognitive Neuroscience

The Biology of the Mind

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With special appreciation for the Fifth Edition to Rebecca A. Gazzaniga, MD



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Composition: MPS North America LLC

Illustrations: Quade Paul, Echo Medical Media LLC

Manufacturing: Transcontinental Interglobe—Beauceville, Quebec

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Library of Congress Cataloging-in-Publication Data

Names: Gazzaniga, Michael S., author. | Ivry, Richard B., author. | Mangun, G. R. (George Ronald), 1956- author.
Title: Cognitive neuroscience : the biology of the mind / Michael S. Gazzaniga, University of California, Santa Barbara, Richard B. Ivry, University of California, Berkeley, George R. Mangun, University of California, Davis ; with special appreciation for the fifth edition to Rebecca A. Gazzaniga, M.D.
Description: Fifth edition. | New York : W.W. Norton & Company, 2019. | Includes bibliographical references and index.
Identifiers: LCCN 2018039129 | **ISBN 9780393603170 (hardcover)**
Subjects: LCSH: Cognitive neuroscience.
Classification: LCC QP360.5 .G39 2019 | DDC 612.8/233—dc23 LC record available at https://lccn.loc.gov/2018039129

W. W. Norton & Company, Inc., 500 Fifth Avenue, New York, NY 10110
wwnorton.com
W. W. Norton & Company Ltd., 15 Carlisle Street, London W1D 3BS

1 2 3 4 5 6 7 8 9 0

For Lilly, Emmy, Garth, Dante,
Rebecca, and Leonardo
M.S.G.

For Henry and Sam
R.B.I.

For Nicholas and Alexander
G.R.M.

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Preface

Welcome to the Fifth Edition! When cognitive neuroscience emerged in the late 1970s, it remained to be seen whether this new field would have "legs." Today, the answer is clear: the field has blossomed in spectacular fashion. Cognitive neuroscience is well represented at all research universities, providing researchers and graduate students with the tools and opportunities to develop the interdisciplinary research programs that are the mainstay of the field. Multiple journals, some designed to cover the entire field, and others specialized for particular methodologies or research themes, have been launched to provide venues to report the latest findings. The number of papers increases at an exponential rate. The Cognitive Neuroscience Society has also flourished and just celebrated its 25th year.

The fundamental challenge we faced in laying the groundwork for our early editions was to determine the basic principles that make cognitive neuroscience distinct from physiological psychology, neuroscience, cognitive psychology, and neuropsychology. It is now obvious that cognitive neuroscience overlaps with, and synthesizes, these disciplinary approaches as researchers aim to understand the neural bases of cognition. In addition, cognitive neuroscience increasingly informs and is informed by disciplines outside the mind–brain sciences, such as systems science and physics, as exemplified by our new Chapter 14: "The Consciousness Problem."

As in previous editions of this book, we continue to seek a balance between psychological theory, with its focus on the mind, and the neuropsychological and neuroscientific evidence about the brain that informs this theory. We make liberal use of patient case studies to illustrate essential points and observations that provide keys to understanding the architecture of cognition, rather than providing an exhaustive description of brain disorders. In every section, we strive to include the most current information and theoretical views, supported by evidence from the cutting-edge technologies that are such a driving force in cognitive neuroscience. In contrast to purely cognitive or neuropsychological approaches, this text emphasizes the convergence of evidence that is a crucial aspect of any science, particularly studies of higher mental function. To complete the story, we also provide examples of research that uses computational techniques.

Teaching students to think and ask questions like cognitive neuroscientists is a major goal of our text. As cognitive neuroscientists, we examine mind–brain relationships using a wide range of techniques, such as functional and structural brain imaging, neurophysiological recording in animals, human EEG and MEG recording, brain stimulation methods, and analysis of syndromes resulting from brain damage. We highlight the strengths and weaknesses of these methods to demonstrate how these techniques must be used in a complementary manner.

We want our readers to learn what questions to ask, how to choose the tools and design experiments to answer these questions, and how to evaluate and interpret the results of those experiments. Despite the stunning progress of the neurosciences, the brain remains a great mystery, with each insight inspiring new questions. For this reason, we have not used a declarative style of writing throughout the book. Instead, we tend to present results that can be interpreted in more than one way, helping the reader to recognize that alternative interpretations are possible.

Since the first edition, there have been many major technological, methodological, and theoretical developments. There has been an explosion of brain-imaging studies; indeed, thousands of functional imaging studies are published each year. New technologies used for noninvasive brain stimulation, magnetic resonance spectroscopy, electrocorticography, and optogenetics have been added to the arsenal of the cognitive neuroscientist. Fascinating links to genetics, comparative anatomy, computation, and robotics have emerged. Parsing all of these studies and deciding which ones should be included has been a major challenge for us. We firmly believe that technology is a cornerstone of scientific advancement. Thus we have felt it essential to capture the cutting-edge trends in the field, while keeping in mind that this is an undergraduate survey text.

The first four editions provide compelling evidence that our efforts have led to a highly useful text for undergraduates taking their first course in cognitive neuroscience, as well as a concise reference volume for graduate students and researchers. Over 500 colleges and universities worldwide have adopted the text. Moreover, instructors tell us that in addition to our interdisciplinary

approach, they like that our book has a strong narrative voice and offers a manageable number of chapters to teach in a one-semester survey course.

With every revised edition including this one, we have had to do some pruning and considerable updating to stay current with all of the developments in the field of cognitive neuroscience. We thought it essential to include new methods and, correspondingly, new insights that these tools have provided into the function of the brain, while being selective in the description of specific experimental results. The following table lists the major changes for each chapter.

Chapter	Changes in the Fifth Edition
1. A Brief History of Cognitive Neuroscience	Expanded discussion of the theoretical leap made by the early Greeks that enabled scientific endeavors. Added discussion of monism versus dualism and the mind–brain problem.
2. Structure and Function of the Nervous System	Added discussion of specific neurotransmitters. Added discussion of neural circuits, networks, and systems. Expanded discussion of the cortex from the viewpoint of functional subtypes. Added discussion of neurogenesis throughout the life span.
3. Methods of Cognitive Neuroscience	Updated discussion of direct and indirect stimulation methods used to probe brain function and as a tool for rehabilitation. Expanded discussion of electrocorticography. Added discussion of new methods to analyze fMRI data, including measures of connectivity. Added section on magnetic resonance spectroscopy.
4. Hemispheric Specialization	Expanded discussion of the problem of cross-cuing when evaluating the performance of split-brain patients. Added discussion of differing patterns of functional connectivity in the right and left hemispheres. Added discussion of atypical patterns of hemispheric lateralization. Expanded section on modularity.
5. Sensation and Perception	Added section on olfaction, tears, and sexual arousal. Added review of new concepts regarding gustatory maps in the cortex. Expanded section on perceptual and cortical reorganization after sensory loss. Added section on cochlear implants.
6. Object Recognition	Added section on decoding the perceptual content of dreams. Added discussion of deep neural networks as a model of the hierarchical organization of visual processing. Added section on feedback mechanisms in object recognition. Expanded section on category specificity.
7. Attention	Expanded discussion of neural oscillations and neural synchrony and attention. Updated discussion of pulvinar contributions to attentional modulation and control.
8. Action	Expanded discussion of the recovery from stroke. Updated with latest findings in research on brain–machine interface systems. Updated discussion of deep brain stimulation and Parkinson's disease. Added discussion of the contributions of the cortex and subcortex to skilled motor movement.

Chapter	Changes in the Fifth Edition
9. Memory	Added brief section on dementias.
	Added discussion of the contribution of corticobasal ganglia loops to procedural memory.
	Expanded discussion of priming and amnesia.
	Updated discussion of frontal cortex activity and memory formation.
	Added brief section on learning while sleeping.
	Updated discussion of an unexpected finding concerning the cellular mechanisms of memory storage.
10. Emotion	Added section on the hypothalamic-pituitary-adrenal axis.
	Added discussion of theoretical disagreements between researchers of human emotion and nonhuman animal emotion.
	Added brief discussion of the role of the periaqueductal gray in emotion.
	Updated discussion of emotion and decision making.
11. Language	Added brief description of connectome-based lesion-symptom mapping for aphasic patients.
	Added section on feedback control and speech production.
	Updated discussion of language evolution in primates.
	Added investigation of how the brain represents semantic information.
12. Cognitive Control	Added section on cognitive control issues associated with neuropsychiatric disorders.
	Expanded discussion of decision making and reward signals in the brain.
	Added section on brain training to improve cognitive control.
13. Social Cognition	Added brief section on the development of social cognition.
	Added brief discussion of social isolation.
	Updated section on autism spectrum disorder.
	Updated discussion of the default network and social cognition.
	Added section on embodiment and visual body illusions, and body integrity identity disorder.
14. The Consciousness Problem	Added section on levels of arousal.
	Added section on the layered architecture of complex systems.
	Added discussion of sentience versus the content of conscious experience.
	Added discussion of the principle of complementarity in physics and how it may apply to the mind–brain problem.

Inspired by feedback from our adopters, we have also made the text even more user-friendly and focused on the takeaway points. Some ways in which we have made the Fifth Edition more accessible include the following:

- Each chapter now begins with a series of "Big Questions" to frame the key themes of the chapter.
- The introductory stories have been trimmed, and many of them feature patient case studies to engage students.
- "Anatomical Orientation" figures open Chapters 4 through 14 to highlight the brain anatomy that will be addressed in the pages that follow.
- Major section headings have been numbered for easy assigning. Each section ends with a set of bulleted "Take-Home Messages."
- Figure captions have been made more concise and more focused on the central teaching point.
- Two new types of boxes ("Lessons from the Clinic" and "Hot Science") feature clinical and research examples in cognitive neuroscience.

As with each edition, this book is the result of a dynamic yet laborious interactive effort among the three of us, along with extensive discussions with our colleagues, our students, and our reviewers. The product has benefited immeasurably from these interactions. Of course, we are ready to modify and improve any and all of our work. In our earlier editions, we asked readers to contact us with suggestions and questions, and we do so again. We live in an age where interaction is swift and easy. We are to be found as follows: gazzaniga@ucsb.edu; mangun@ucdavis.edu; ivry@berkeley.edu.

Good reading and learning!

Acknowledgments

Once again, we are indebted to a number of people. First and foremost we would like to thank Rebecca A. Gazzaniga, MD, for her extensive and savvy editing of the Fifth Edition. She mastered every chapter, with an eye to making sure that the story was clear and engaging. We could not have completed this edition without her superb scholarship and editing skills.

The Fifth Edition also benefited from the advice of various specialists in the field of cognitive neuroscience. Karolina Lampert at the University of Pennsylvania assisted us with the study of emotion. Carolyn Parkinson at UCLA helped update our chapter on social cognition. Nikkie Marinsek from UC Santa Barbara did the same for the topic of lateralization. Geoff Woodman from Vanderbilt University and Sabine Kastner from Princeton provided valuable advice on attention. Arne Ekstrom, Charan Ranganath, Brian Wilgen, and Andy Yonelinas from UC Davis; Ken Paller from Northwestern University; Nancy A. Dennis from Pennsylvania State University; and Michael Miller from UC Santa Barbara provided numerous insights about memory. Ellen F. Lau from the University of Maryland, Gina Kuperberg from Tufts University and Massachusetts General Hospital, Alexander Huth and Jack Gallant from UC Berkeley, David Corina from UC Davis, and Jeffrey Binder from the Medical College of Wisconsin advised us on mechanisms of language and semantic representation. For answering miscellaneous questions that cropped up in the methods chapter, we tip our hats to Scott Grafton from UC Santa Barbara and Danielle Bassett from the University of Pennsylvania. For the perception and object recognition chapters, David Somers from Boston University, as well as Jack Gallant (again!) and Kevin Weiner from UC Berkeley, gave useful advice and supplied us with beautiful graphics.

We are also especially grateful to Tamara Y. Swaab, PhD (UC Davis), for the language chapter in this and prior editions; Michael B. Miller, PhD (UC Santa Barbara), for contributions to the chapter on hemispheric lateralization; and Stephanie Cacioppo, PhD (University of Chicago), for contributions to the chapter on emotion.

For work on the previous editions that continues to play an active part in this new edition, we thank again Megan Steven (Dartmouth College), Jeff Hutsler (University of Nevada, Reno), and Leah Krubitzer (UC Davis) for evolutionary perspectives; Jennifer Beer (University of Texas at Austin) for insights on social cognition; and Liz Phelps (New York University) for her work on emotion. Tim Justus (Pitzer College) is to be thanked for sharing his advice and wisdom, and for helping along the way. Also Jason Mitchell, PhD (Harvard University), for contributions to the social cognition chapter. We thank Frank Forney for his art in the previous editions, and Echo Medical Media for the new art in the fourth and fifth editions. We also thank our many colleagues who provided original artwork or scientific figures. We would also like to thank our readers Annik Carson and Mette Clausen-Bruun, who took the time to point out typos in our previous edition; to anatomist Carlos Avendaño, who alerted us to some anatomical errors; and to Sophie van Roijen, who suggested the very good idea of adding an index of abbreviations.

Several instructors took time from their busy schedules to review our previous edition and make suggestions for the Fifth Edition. We thank the following:

Maxwell Bertolero, *University of California, Berkeley*
Flavia Cardini, *Anglia Ruskin University*
Joshua Carlson, *Northern Michigan University*
Tim Curran, *University of Colorado, Boulder*
Mark D'Esposito, *University of California, Berkeley*
Karin H. James, *Indiana University*
Mark Kohler, *University of South Australia*
Bruno Laeng, *University of Oslo, Norway*
Karolina M. Lempert, *University of Pennsylvania*
Carolyn Parkinson, *University of California, Los Angeles*
David Somers, *Boston University*
Weiwei Zhang, *University of California, Riverside*

In addition, we are indebted to many scientists and personal friends. Writing a textbook is a major commitment of time, intellect, and affect! Those who helped significantly are noted below. Some reviewed our words and critiqued our thoughts. Others allowed us to interview them. To all those listed here who reviewed past and present editions or media, we owe our deep gratitude and thanks.

Eyal Aharoni, *Georgia State University*
David G. Amaral, *University of California, Davis*
Franklin R. Amthor, *University of Alabama, Birmingham*

Michael Anderson, *University of Cambridge*
Adam Aron, *University of California, San Diego*
Ignacio Badiola, *University of Pennsylvania*
David Badre, *Brown University*
Juliana Baldo, *VA Medical Center, Martinez, California*
Gary Banker, *Oregon Health Sciences University*
Horace Barlow, *University of Cambridge*
Danielle Bassett, *University of Pennsylvania*
Kathleen Baynes, *University of California, Davis*
N. P. Bechtereva, *Russian Academy of Sciences*
Mark Beeman, *Northwestern University*
Jennifer Beer, *University of Texas at Austin*
Marlene Behrmann, *Carnegie Mellon University*
Maxwell Bertolero, *University of California, Berkeley*
Jeffrey Binder, *Medical College of Wisconsin*
Robert S. Blumenfeld, *California State Polytechnic University, Pomona*
Elizabeth Brannon, *University of Pennsylvania*
Rainer Breitling, *University of Manchester*
Silvia Bunge, *University of California, Berkeley*
Stephanie Cacioppo, *University of Chicago*
Flavia Cardini, *Anglia Ruskin University*
Joshua Carlson, *Northern Michigan University*
Valerie Clark, *University of California, Davis*
Clay Clayworth, *University of California, Berkeley*
Asher Cohen, *Hebrew University*
Jonathan Cohen, *Princeton University*
Roshan Cools, *Radboud University, Nijmegen*
J. M. Coquery, *Université des Sciences et Technologies de Lille*
Michael Corballis, *University of Auckland*
Paul Corballis, *University of Auckland*
David Corina, *University of California, Davis*
Tim Curran, *University of Colorado, Boulder*
Clayton Curtis, *New York University*
Anders Dale, *University of California, San Diego*
Antonio Damasio, *University of Southern California*
Hanna Damasio, *University of Southern California*
Lila Davachi, *New York University*
Daniel C. Dennett, *Tufts University*
Nancy A. Dennis, *Pennsylvania State University*
Michel Desmurget, *Centre de Neuroscience Cognitive*
Mark D'Esposito, *University of California, Berkeley*
Joern Diedrichsen, *University of Western Ontario*
Nina Dronkers, *University of California, Davis*
Arne Ekstrom, *University of California, Davis*
Paul Eling, *Radboud University, Nijmegen*
Russell Epstein, *University of Pennsylvania*
Martha Farah, *University of Pennsylvania*
Harlan Fichtenholtz, *Keene State College*
Peter T. Fox, *University of Texas*
Karl Friston, *University College London*
Rusty Gage, *Salk Institute*
Jack Gallant, *University of California, Berkeley*
Vittorio Gallese, *University of Parma, Italy*
Isabel Gauthier, *Vanderbilt University*
Christian Gerlach, *University of Southern Denmark*
Robbin Gibb, *University of Lethbridge*
Gail Goodman, *University of California, Davis*
Elizabeth Gould, *Princeton University*
Jay E. Gould, *University of West Florida*
Scott Grafton, *University of California, Santa Barbara*
Charlie Gross, *Princeton University*
Nouchine Hadjikhani, *Massachusetts General Hospital*
Peter Hagoort, *Max Planck Institute for Psycholinguistics*
Todd Handy, *University of British Columbia*
Jasmeet Pannu Hayes, *Boston University*
Eliot Hazeltine, *University of Iowa*
Hans-Jochen Heinze, *University of Magdeburg*
Arturo Hernandez, *University of Houston*
Laura Hieber Adery, *Vanderbilt University*
Steven A. Hillyard, *University of California, San Diego*
Hermann Hinrichs, *University of Magdeburg*
Jens-Max Hopf, *University of Magdeburg*
Joseph Hopfinger, *University of North Carolina, Chapel Hill*
Richard Howard, *National University of Singapore*
Drew Hudson, *University of California, Berkeley*
Jeffrey Hutsler, *University of Nevada, Reno*
Alexander Huth, *University of Texas at Austin*
Akira Ishiguchi, *Ochanomizu University*
Lucy Jacobs, *University of California, Berkeley*
Karin H. James, *Indiana University*
Amishi Jha, *University of Miami*
Cindy Jordan, *Michigan State University*
Tim Justus, *Pitzer College*
Nancy Kanwisher, *Massachusetts Institute of Technology*
Sabine Kastner, *Princeton University*
Larry Katz, *Harvard University*
Steven Keele, *University of Oregon*
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Bruno Laeng, *University of Oslo, Norway*

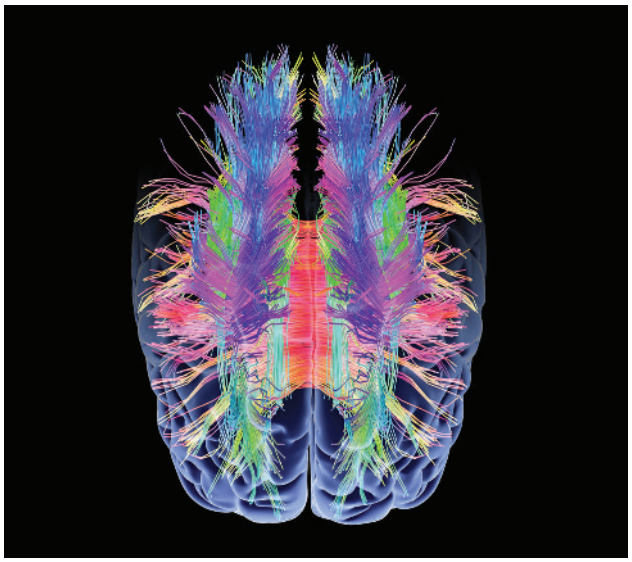
Ayelet Landau, *Hebrew University*
Ellen F. Lau, *University of Maryland*
Joseph E. Le Doux, *New York University*
Karolina M. Lempert, *University of Pennsylvania*
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Nikki Marinsek, *University of California, Santa Barbara*
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Teresa Mitchell, *University of Massachusetts*
Ryan Morehead, *Harvard University*
Amy Needham, *Vanderbilt University*
Kevin Ochsner, *Columbia University*
Ken A. Paller, *Northwestern University*
Galina V. Paramei, *Liverpool Hope University*
Carolyn Parkinson, *University of California, Los Angeles*
Steven E. Petersen, *Washington University in St. Louis*
Liz Phelps, *New York University*
Steven Pinker, *Harvard University*
Lara Polse, *University of California, San Diego*
Michael I. Posner, *University of Oregon*
David Presti, *University of California, Berkeley*
Robert Rafal, *University of Delaware*
Marcus Raichle, *Washington University School of Medicine*
Charan Ranganath, *University of California, Davis*
Patricia Reuter-Lorenz, *University of Michigan*
Jesse Rissman, *University of California, Los Angeles*
Leah Roesch, *Emory University*
Matthew Rushworth, *University of Oxford*
Kim Russo, *University of California, Davis*
Alexander Sack, *Maastricht University*
Mikko E. Sams, *Aalto University*
Donatella Scabini, *University of California, Berkeley*
Daniel Schacter, *Harvard University*
Ariel Schoenfeld, *University of Magdeburg*
Michael Scholz, *University of Magdeburg*
Art Shimamura, *University of California, Berkeley*
Michael Silver, *University of California, Berkeley*
Michael Silverman, *Simon Fraser University*
Noam Sobel, *Weizmann Institute of Science*
David Somers, *Boston University*
Allen W. Song, *Duke University*
Larry Squire, *University of California, San Diego*
Alit Stark-Inbar, *University of California, Berkeley*
Michael Starks, *3DTV Corporation*
Megan Steven, *Dartmouth College*
Tamara Y. Swaab, *University of California, Davis*
Thomas M. Talavage, *Purdue University*
Keiji Tanaka, *Riken Institute*
Michael Tarr, *Carnegie Mellon University*
Jordan Taylor, *Princeton University*
Sharon L. Thompson-Schill, *University of Pennsylvania*
Roger Tootell, *Massachusetts General Hospital*
Carrie Trutt, *Duke University*
Endel Tulving, *Rotman Research Institute, Baycrest Center*
Kevin Weiner, *University of California, Berkeley*
C. Mark Wessinger, *University of Nevada, Reno*
Megan Wheeler, *Eric Schmidt Foundation*
Susanne Wiking, *University of Tromsø*
Kevin Wilson, *Gettysburg College*
Brian Wiltgen, *University of California, Davis*
Ginger Withers, *Whitman College*
Marty G. Woldorff, *Duke University*
Geoff Woodman, *Vanderbilt University*
Andrew Yonelinas, *University of California, Davis*
Weiwei Zhang, *University of California, Riverside*

Often we forget to thank the many participants in the research work that we discuss, some of whom have generously given hundreds of hours of their time. Without their contributions, cognitive neuroscience would not be where it is today.

Finally, we would like to thank the outstanding editorial and production team at W. W. Norton: Sheri Snavely, Andrew Sobel, Carla Talmadge, Ben Reynolds, Kaitlin Coats, Tori Reuter, Eve Sanoussi, Allison Smith, and Stephanie Hiebert, whose sharp eyes and wise counsel have helped us produce this exciting new edition of our textbook.

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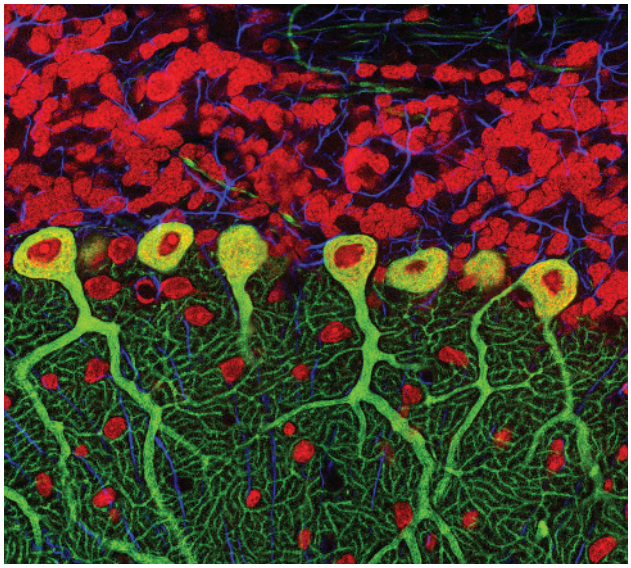
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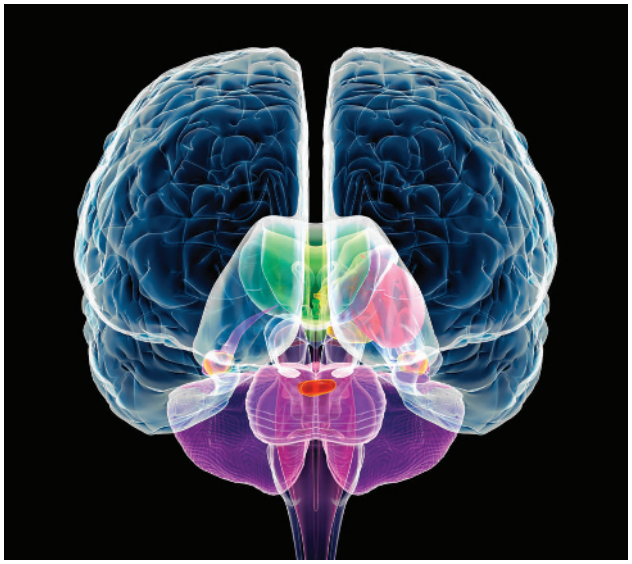
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FIFTH EDITION

Cognitive Neuroscience

The Biology of the Mind



In science it often happens that scientists say, "You know that's a really good argument; my position is mistaken," and then they actually change their minds and you never hear that old view from them again. They really do it. It doesn't happen as often as it should, because scientists are human and change is sometimes painful. But it happens every day. I cannot recall the last time something like that happened in politics or religion.

Carl Sagan, 1987

CHAPTER

1

A Brief History of Cognitive Neuroscience

ANNE GREEN WALKED to the gallows in the castle yard of Oxford, England, in 1650, about to be executed for a crime she had not committed: murdering her stillborn child. No doubt she felt scared, angry, and frustrated, and many thoughts raced through her head. However, "I am about to play a role in the founding of clinical neurology and neuroanatomy"—though accurate—certainly was not one of them. She proclaimed her innocence to the crowd, a psalm was read, and she was hanged. She hung there for a full half hour before she was taken down, pronounced dead, and placed in a coffin provided by Drs. Thomas Willis and William Petty. This was when her luck began to improve. Willis and Petty were physicians and had been given permission from King Charles I to dissect, for medical research, the bodies of any criminals killed within 21 miles of Oxford. So, instead of being buried, Green's body was carried to their office.

An autopsy, however, was not what took place. As if in a scene from Edgar Allan Poe, the coffin began to emit a grumbling sound. Green was alive! The doctors poured spirits in her mouth and rubbed a feather on her neck to make her cough. They rubbed her hands and feet for several minutes, bled 5 ounces of blood, swabbed her neck wounds with turpentine, and cared for her through the night. The next morning, feeling more chipper, she asked for a beer. Five days later, she was out of bed and eating normally (Molnar, 2004; Zimmer, 2004).

After her ordeal, the authorities wanted to hang Green again. But Willis and Petty fought in her defense, arguing that her baby had been stillborn and its death was not her fault. They declared that divine providence had stepped in and provided her miraculous escape from death, thus proving her innocence. Their arguments prevailed. Green was set free and went on to marry and have three more children.

This miraculous incident was well publicized in England (**Figure 1.1**). Thomas Willis (**Figure 1.2**) owed much to Anne Green and the fame brought to him by the events of her resurrection. With it came money he desperately needed and the

BIG Questions

- Why were the ancient Greeks important to science?
- What historical evidence suggested that the brain's activities produce the mind?
- What can we learn about the mind and brain from modern research methods?



FIGURE 1.1
An artistic rendition of the miraculous resurrection of Anne Green in 1650.

prestige to publish his work and disseminate his ideas, and he had some good ones. Willis became one of the best-known doctors of his time: He coined the term *neurology*, and he was the first anatomist to link specific brain damage—that is, changes in brain structure—to specific behavioral deficits and to theorize how the brain transfers information. He drew these conclusions after treating patients throughout their lives and autopsying them after their deaths.

With his colleague and friend Christopher Wren (the architect who designed St. Paul's Cathedral in London), Willis created drawings of the human brain that remained the most accurate representations for 200 years (**Figure 1.3**). He also coined names for numerous brain regions (**Table 1.1**; Molnar, 2004; Zimmer, 2004). In short, Willis set in motion the ideas and knowledge base that took hundreds of years to develop into what we know today as the field of cognitive neuroscience.



FIGURE 1.2
Thomas Willis (1621–1675), a founder of clinical neuroscience.

In this chapter we discuss some of the scientists and physicians who have made important contributions to this field. You will discover the origins of cognitive neuroscience and how it has developed into what it is today: a discipline geared toward understanding how the brain works, how brain structure and function affect behavior, and ultimately how the brain enables the mind.

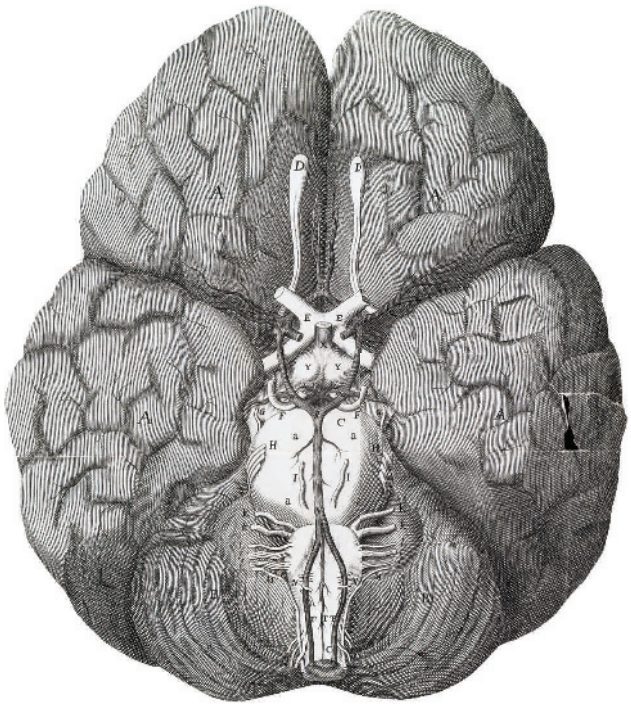


FIGURE 1.3 The human brain (ventral view) drawn by Christopher Wren.
Wren made drawings for Thomas Willis's *Anatomy of the Brain and Nerves*. The circle of dark vessels in the very center of the drawing was named the circle of Willis by one of Willis's students, Richard Lower.

1.1 A Historical Perspective

The scientific field of **cognitive neuroscience** received its name in the late 1970s in the back seat of a New York City taxi. One of us (M.S.G.) was riding with the great cognitive psychologist George A. Miller on the way to a dinner meeting at the Algonquin Hotel. The dinner was being held for scientists from Rockefeller and Cornell universities, who were joining forces to study how the brain enables the mind—a subject in need of a name. Out of that taxi ride came the term *cognitive neuroscience*—from *cognition*, or the process of knowing (i.e., what arises from awareness, perception, and reasoning), and *neuroscience* (the study of how the nervous system is organized and functions). This seemed the perfect term to describe the question of understanding how the functions of the physical brain can yield the thoughts, ideas, and beliefs of a seemingly intangible mind. And so the term took hold in the scientific community.

When considering the miraculous properties of brain function, bear in mind that Mother Nature built our brains through the process of evolution by natural selection. Unlike computers, our brains were designed not by a team of rational engineers, but through trial and error, and they are made of living cells, not inert substances.

TABLE 1.1 A Selection of Terms Coined by Thomas Willis

Term	Definition
Anterior commissure	Axonal fibers connecting the middle and inferior temporal gyri of the left and right hemispheres.
Cerebellar peduncles	Axonal fibers connecting the cerebellum and brainstem.
Claustrum	A thin sheath of gray matter located between two brain areas: the external capsule and the putamen.
Corpus striatum	A part of the basal ganglia consisting of the caudate nucleus and the lenticular nucleus.
Inferior olives	The part of the brainstem that modulates cerebellar processing.
Internal capsule	White matter pathways conveying information from the thalamus to the cortex.
Medullary pyramids	A part of the medulla that consists of corticospinal fibers.
Neurology	The study of the nervous system and its disorders.
Optic thalamus	The portion of the thalamus relating to visual processing.
Spinal accessory nerve	The 11th cranial nerve, which innervates the head and shoulders.
Stria terminalis	The white matter pathway that sends information from the amygdala to the basal forebrain.
Striatum	Gray matter structure of the basal ganglia.
Vagus nerve	The 10th cranial nerve, which, among other functions, has visceral motor control of the heart.

We must keep both these things in mind when we try to understand the brain's architecture and function.

Life first appeared on our 4.5-billion-year-old Earth approximately 3.8 billion years ago, but human brains, in their present form, have been around for only about 100,000 years, a mere drop in the bucket. The primate brain appeared between 34 million and 23 million years ago, during the Oligocene epoch. It evolved into the progressively larger brains of the great apes in the Miocene epoch between roughly 23 million and 7 million years ago. The human lineage diverged from the last common ancestor that we shared with the chimpanzee somewhere in the range of 5 million to 7 million years ago. Since that divergence, our brains have evolved into the present human brain, capable of all sorts of wondrous feats.

Throughout this book, we will be reminding you to take the evolutionary perspective: Why might this behavior have been selected for? How could it have promoted survival and reproduction? WWHGD? (What would a hunter-gatherer do?) The evolutionary perspective often helps us to ask more informed questions and provides insight into how and why the brain functions as it does.

During most of our history, life was given over to the practical matter of survival. Nonetheless, the brain mechanisms that enable us to generate theories about the characteristics of human nature thrived inside the heads of ancient humans. As civilization developed, our ancestors began to spend time looking for causes of and constructing complex theories about the motives of fellow humans. But in these early societies, people thought of the natural world just as they thought of themselves—having thoughts, desires, and emotions.

It was the ancient Greeks who made the theoretical leap to the view that we are separate from the world we occupy. This delineation allowed them to conceive of the natural world as an object, an "it" that could be studied objectively—that is, scientifically. Egyptologist Henri Frankfort called this leap "breath-taking": "These men proceeded, with preposterous boldness on an entirely unproved assumption. They held that the universe is an intelligible whole. In other words, they presumed that a single order underlies the chaos of our perceptions and, furthermore, that we are able to comprehend that order" (Frankfort et al., 1977). The pre-Socratic Greek philosopher Thales, presaging modern cognitive neuroscience, rejected supernatural explanations of phenomena and proclaimed that every event had a natural cause. But on the subject of cognition, the early Greeks were limited in what they could say: They did not have the methodology to systematically explore the brain and the thoughts it produces (the mind) through experimentation.

Over the past 2,500 years, there has been an underlying tension between two ideas concerning the brain and the conscious mind. Thales represents one perspective, which posits that the flesh-and-blood brain produces thoughts—a stance known as *monism*. René Descartes (**Figure 1.4**), the 17th-century French philosopher, mathematician, and scientist, is known for the other. He believed that the body (including the brain) had material properties and worked like a machine, whereas the mind was nonmaterial and thus did not follow the laws of nature (i.e., Newton's laws of physics). Even so,



FIGURE 1.4
René Descartes (1596–1650). Portrait by Frans Hals.

he thought that the two interacted: The mind could influence the body and, through "the passions," the body could influence the mind. He had a difficult time figuring out where this interaction occurred but decided it must have been inside a single brain structure (i.e., not one found bilaterally), and the pineal gland was all that he could find that fit this description, so he settled on it. Descartes's stance that the mind appears from elsewhere and is not the result of the machinations of the brain is known as *dualism.*

Cognitive neuroscience takes Thales's monistic perspective that the conscious mind is a product of the brain's physical activity and not separate from it. We will see that evidence for this view initially came from studying patients with brain lesions, and later from scientific investigations.

The modern tradition of observing, manipulating, and measuring became the norm in the 19th century as scientists started to determine how the brain gets its jobs done. To understand how biological systems work, we must make an observation, ask why it came about, form a hypothesis, design and perform an experiment that will either support or refute that hypothesis, and, finally, draw a conclusion. Then, ideally, a different researcher reads our work, replicates the experiment, and obtains the same findings. If not, then the topic needs to be revisited. This approach is known as the *scientific method*, and it is the only way that a topic can move along on sure footing. And in the case of cognitive neuroscience, there is no end of rich phenomena to study.

1.2 The Brain Story

Imagine that you are given a problem to solve. A hunk of biological tissue is known to think, remember, attend, solve problems, tell jokes, want sex, join clubs, write novels, exhibit bias, feel guilty, and do a zillion other things. You are supposed to figure out how it works. You might start by looking at the big picture and asking yourself a couple of questions. "Hmm, does the blob work as a unit, with each part contributing to a whole? Or is the blob full of individual processing parts, each carrying out specific functions, so the result is something that looks like it is acting as a whole unit?" From a distance, the city of New York (another type of blob) appears as an integrated whole, but it is actually composed of millions of individual processors—that is, people. Perhaps people, in turn, are made of smaller, more specialized units.

This central issue—whether the mind is enabled by the whole brain working in concert or by specialized parts of the brain working at least partly independently—is what fuels much of modern research in cognitive neuroscience. As we will see, the dominant view has changed back and forth over the years, and it continues to change today.

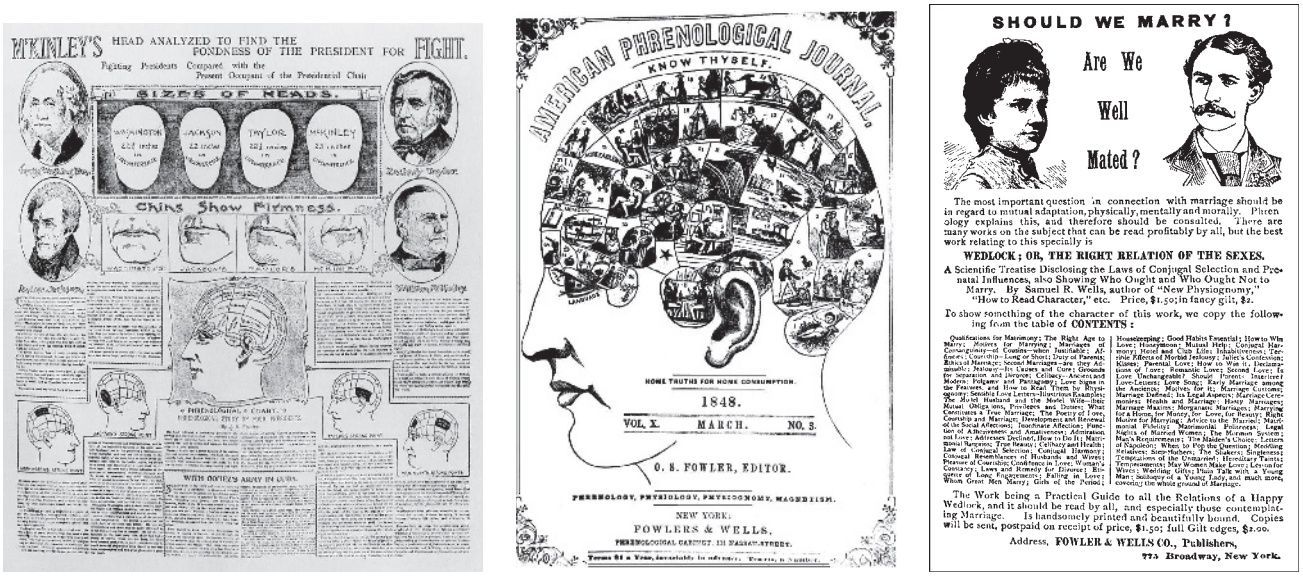
Thomas Willis foreshadowed cognitive neuroscience with the notion that isolated brain damage (biology) could affect behavior (psychology), but his insights slipped from view. It took another century for Willis's ideas to resurface. They were expanded upon by a young Austrian physician and neuroanatomist, Franz Joseph Gall (**Figure 1.5**). After studying numerous patients, Gall became convinced that the brain was the organ of the mind and that innate faculties were localized in specific regions of the cerebral cortex. He thought that the brain was organized around some 35 or more specific functions, ranging from cognitive basics such as language and color perception to more ephemeral capacities such as affection and a moral sense, and that each was supported by specific brain regions. These ideas were well received, and Gall took his theory on the road, lecturing throughout Europe.



FIGURE 1.5
Franz Joseph Gall (1758–1828), one of the founders of phrenology.

Gall and his disciple, Johann Spurzheim, hypothesized that if a person used one of the faculties with greater frequency than the others, the part of the brain representing that function would grow (Gall & Spurzheim, 1810–1819). This increase in local brain size would cause a bump in the overlying skull. Logically, then, Gall and his colleagues believed that a careful analysis of the skull could go a long way in describing the personality of the person inside the skull. Gall called this technique *anatomical personology.* The idea that character could be divined through palpating the skull was dubbed **phrenology** by Spurzheim and, as you may well imagine, soon fell into the hands of charlatans (**Figure 1.6**). Some employers even required job applicants to have their skulls "read" before they were hired.

Gall, apparently, was not politically astute. When asked to read the skull of Napoleon Bonaparte, he did not ascribe to it the noble characteristics that the future emperor was sure he possessed. When Gall later applied to the Academy of Sciences of Paris, Napoleon decided that phrenology needed closer scrutiny and ordered the academy to obtain some scientific evidence of its validity. Although Gall was a physician and neuroanatomist, he was not a scientist. He observed correlations and sought only to confirm, not disprove, them. The academy asked physiologist Marie-Jean-Pierre Flourens (**Figure 1.7**) to see whether he could come up with any concrete findings that could back up this theory.



a b c

FIGURE 1.6 Phrenology goes mainstream.
(a) An analysis of Presidents Washington, Jackson, Taylor, and McKinley by Jessie A. Fowler, from the *Phrenological Journal*, June 1898. **(b)** The phrenological map of personal characteristics on the skull, from the *American Phrenological Journal*, March 1848. **(c)** Fowler & Wells Co. publication on marriage compatibility based on phrenology, 1888.

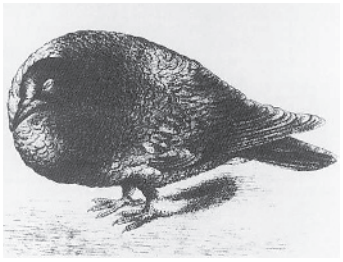
Flourens set to work. He destroyed parts of the brains of pigeons and rabbits and observed what happened. He was the first to show that, indeed, certain parts of the brain were responsible for certain functions. For instance, when he removed the cerebral hemispheres, the animal no longer had perception, motor ability, and judgment. Without the cerebellum, the animals became uncoordinated and lost their equilibrium. He could not, however, find any areas for advanced abilities such as memory or cognition, and he concluded that these were more diffusely scattered throughout the brain.

Flourens developed the notion that the whole brain participated in behavior—a view later known as the **aggregate field theory**. In 1824 Flourens wrote, "All sensations, all perceptions, and all volitions occupy the same seat in these (cerebral) organs. The faculty of sensation, percept and volition is then essentially one faculty." The theory of localized brain functions, known as localizationism, fell out of favor.

That state of affairs didn't last long, however. New evidence started trickling in from across Europe, and the pendulum slowly swung back to the localizationist view. In 1836 a neurologist from Montpellier, Marc Dax, provided one of the first bits. He sent a report to the French Academy of Sciences about three patients, noting that each had similar speech disturbances and similar left-hemisphere lesions found at autopsy. At the time, a report from the provinces got short shrift in Paris, and it would be another 30 years before anyone took much notice of this observation that speech could be disrupted by a specific lesion in the left hemisphere.

Meanwhile, in England, the neurologist John Hughlings Jackson (**Figure 1.8**) began to publish his observations on the behavior of persons with brain damage. A key feature of Jackson's





a b

FIGURE 1.7
(a) Marie-Jean-Pierre Flourens (1794–1867), who supported the idea later termed the *aggregate field theory.* **(b)** The posture of a pigeon deprived of its cerebral hemispheres, as described by Flourens.



FIGURE 1.8
John Hughlings Jackson (1835–1911), an English neurologist who was one of the first to recognize the localizationist view.

BOX 1.1 | LESSONS FROM THE CLINIC

Fits and Starts

If you were unlucky enough to have a neurological ailment before 1860, physicians had no organized way of thinking to make heads or tails of your problem. But that was about to change.

In 1867 John Hughlings Jackson wrote, "One of the most important questions we can ask an epileptic patient is, 'How does the fit begin?'" Before Jackson started shaking things up in the world of neurology, it was generally believed that the cerebral cortex was not excitable, and experimental physiologists had been convinced by Pierre Flourens that the cortex was equipotential, with no localized functions. But Jackson was armed with lessons he had learned from the clinic that disputed these theories. He had observed the progression of some of his patients' seizures and found consistent patterns to them: "I think the mode of beginning makes a great difference as to the march of the fit. When the fit begins in the face, the convulsion involving the arm may go down the limb. . . . When the fit begins in the leg, the convulsion marches up; when the leg is affected after the arm, the convulsion marches down the leg" (J. H. Jackson, 1868).

These observations led to Jackson's many conclusions: The cortex is excitable; seizures begin in a localized region of the cortex, and that particular region defines where the seizure manifests in the body; excitability of the cortex spreads to neighboring regions of the brain and, because the convulsion gradually progresses from one part of the body to the part immediately adjacent, the regions in the brain that correspond to the body parts must also be next to each other. From his clinical observations, Jackson created the conceptual framework for clinical neurophysiology and provided a systematic way to go about diagnosing diseases of the nervous system (York & Steinberg, 2006), which were later backed by experimentation. Throughout this book, we will follow in Jackson's footsteps and provide observations from clinical practice that must be taken into account when forming hypotheses about brain function.

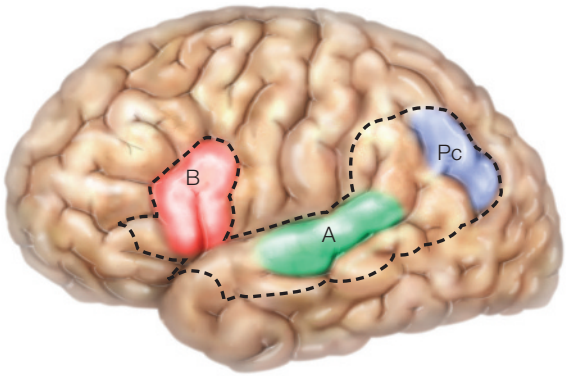
writings was the incorporation of suggestions for experiments to test his observations. He noticed, for example, that during the start of their seizures, some epileptic patients moved in such characteristic ways that the seizure appeared to be stimulating a set map of the body in the brain; that is, the abnormal firings of neurons in the brain produced clonic and tonic jerks in muscles that progressed in the same orderly pattern from one body part to another. This phenomenon led Jackson to propose a *topographic* organization in the cerebral cortex: A map of the body was represented across a particular cortical area, where one part would represent the foot, another the lower leg, and so on (see **Box 1.1**). As we will see, this proposal was verified over a half century later by Wilder Penfield.

Although Jackson was also the first to observe that lesions on the right side of the brain affect visuospatial processes more than do lesions on the left side, he did not maintain that specific parts of the right side of the brain were solely committed to this important human cognitive function. Being an observant clinical neurologist, Jackson noticed that it was rare for a patient to lose a function completely. For example, most people who lost their capacity to speak following a cerebral stroke could still say some words. Patients unable to move their hands voluntarily to specific places on their bodies could still easily scratch those places if they itched. When Jackson made these observations, he concluded that many regions of the brain contribute to a given behavior.

Back in Paris, the well-known and respected physician Paul Broca (**Figure 1.9a**) published, in 1861, the results of his autopsy on a patient who had been nicknamed Tan (his real name was Leborgne)—perhaps the most



a



b

FIGURE 1.9
(a) Paul Broca (1824–1880). **(b)** The connections between the speech centers, from Carl Wernicke's 1876 article on aphasia. A = Wernicke's sensory speech center; B = Broca's area for speech; Pc = Wernicke's area concerned with language comprehension and meaning.

famous neurological case in history. Tan had developed aphasia: He could understand language, but "tan" was the only word he could utter. Broca found that Tan had a syphilitic lesion in his left-hemisphere inferior frontal lobe. This region is now called *Broca's area.* The impact of this finding was huge. Here was a specific aspect of language that was impaired by a specific lesion. Soon Broca had a series of such patients.

This theme was picked up by the German neurologist Carl Wernicke. In 1876 Wernicke reported on a stroke victim who (unlike Broca's patient) could talk quite freely but made little sense when he spoke. Wernicke's patient also could not understand spoken or written language. He had a lesion in a more posterior region of the left hemisphere, an area in and around where the temporal and parietal lobes meet, now referred to as *Wernicke's area* (**Figure 1.9b**).

Today, differences in how the brain responds to focal disease are well known (H. Damasio et al., 2004; Wise, 2003), but over 100 years ago Broca's and Wernicke's discoveries were earth-shattering. (Note that people had largely forgotten Willis's observations that isolated brain damage could affect behavior. Throughout the history of brain science, an unfortunate and oft-repeated trend is that we fail to consider crucial observations made by our predecessors.) With the discoveries of Broca and Wernicke, attention was again paid to this startling point: Focal brain damage causes specific behavioral deficits.

As is so often the case, the study of humans leads to questions for those who work on animal models. Shortly after Broca's discovery, the German physiologists Gustav Fritsch and Eduard Hitzig electrically stimulated discrete parts of a dog brain and observed that this stimulation produced characteristic movements in the dog. This discovery led neuroanatomists to more closely analyze the cerebral cortex and its cellular organization; they wanted support for their ideas about the importance of local regions. Because these regions performed different functions, it followed that they ought to look different at the cellular level.

Going by this logic, German neuroanatomists began to analyze the brain by using microscopic methods to view the cell types in different brain regions. Perhaps the most famous of the group was Korbinian Brodmann, who analyzed the cellular organization of the cortex and characterized 52 distinct regions (**Figure 1.10**). He published his cortical maps in 1909.

Brodmann used tissue stains, such as the one developed by the German neuropathologist Franz Nissl, that permitted him to visualize the different cell types in different brain regions. How cells differ between brain regions is called **cytoarchitectonics**, or *cellular architecture.* Soon, many now famous anatomists—including Oskar Vogt, Vladimir Betz, Theodor Meynert, Constantin von Economo, Gerhardt von Bonin, and Percival Bailey—contributed to this work, and several

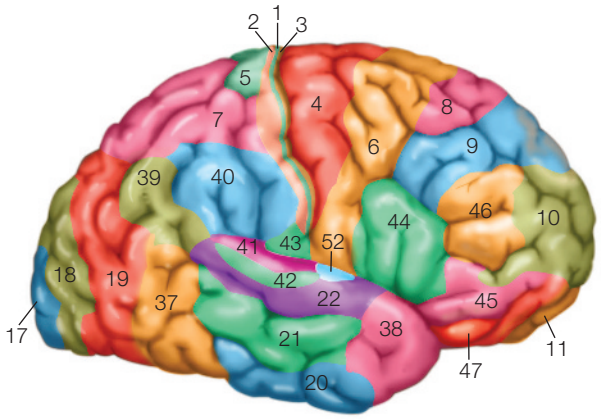
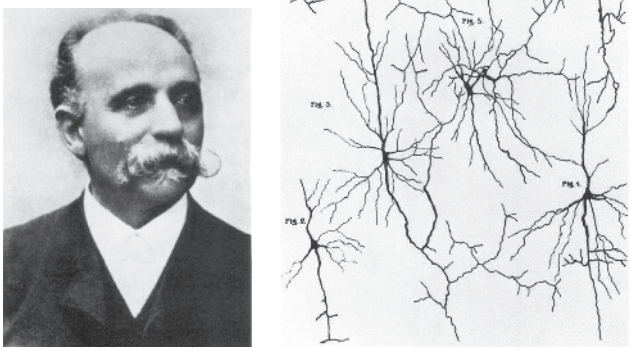


FIGURE 1.10 Brodmann's areas.
Sampling of the 52 distinct areas described by Brodmann on the basis of cell structure and arrangement.

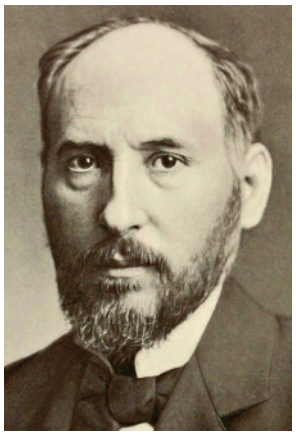
subdivided the cortex even further than Brodmann had. To a large extent, these investigators discovered that various cytoarchitectonically described brain areas do indeed represent functionally distinct brain regions.

Despite all of this groundbreaking work in cytoarchitectonics, the truly huge revolution in our understanding of the nervous system was taking place elsewhere. In Italy and Spain, an intense struggle was going on between two brilliant neuroanatomists. Oddly, it was the work of one that led to the insights of the other. Camillo Golgi (**Figure 1.11**), an Italian physician, developed one of the most famous cell stains in the history of the world: the silver method for staining neurons—*la reazione nera*, "the black reaction"—which impregnated individual neurons with silver chromate. This stain permits visualization of individual neurons in their entirety.

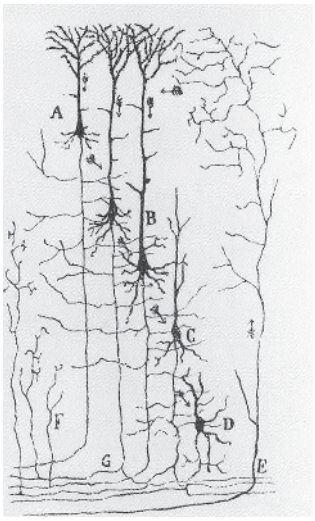


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FIGURE 1.11
(a) Camillo Golgi (1843–1926), cowinner of the 1906 Nobel Prize in Physiology or Medicine. **(b)** Golgi's drawings of different types of ganglion cells in dog and cat.



a



b

FIGURE 1.12
(a) Santiago Ramón y Cajal (1852–1934), cowinner of the 1906 Nobel Prize in Physiology or Medicine. **(b)** Ramón y Cajal's drawing of the afferent inflow to the mammalian cortex.

Using Golgi's method, the Spanish pathologist Santiago Ramón y Cajal (**Figure 1.12**) went on to find that, contrary to the view of Golgi and others, neurons were discrete entities. Golgi had believed that the whole brain was a **syncytium**, a continuous mass of tissue that shares a common cytoplasm. Ramón y Cajal, who some call the father of modern neuroscience, was the first to identify the unitary nature of neurons and to articulate what came to be known as the **neuron doctrine**, the concept that the nervous system is made up of individual cells. He also recognized that the transmission of electrical information went in only one direction, from the dendrites down to the axonal tip (**Figure 1.13**).

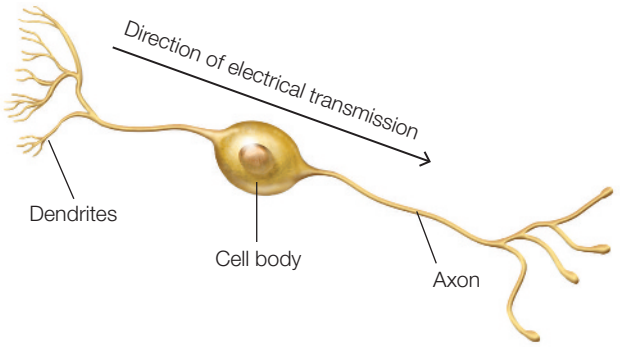
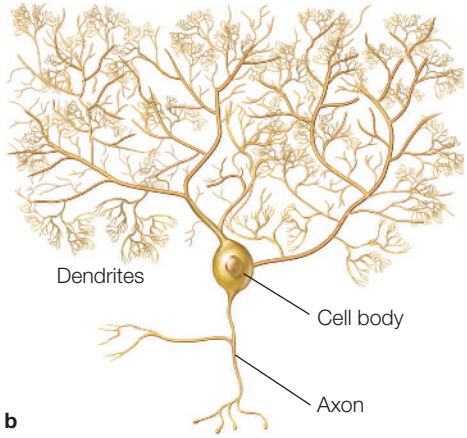


FIGURE 1.13
A bipolar retinal cell, illustrating the dendrites and axon of the neuron.

Many gifted scientists were involved in the early history of the neuron doctrine (Shepherd, 1991). For example, Jan Evangelista Purkinje (**Figure 1.14**), a Czech physiologist, described the first nerve cell in the nervous system in 1837. The German physician and physicist Hermann von Helmholtz (**Figure 1.15**) figured out that electrical current in the cell was not a by-product of cellular activity, but rather the medium that was actually carrying information along the axon of a nerve cell. He was also the first to suggest that invertebrates would be good models for studying vertebrate brain mechanisms. British physiologist Sir Charles Sherrington vigorously pursued the neuron's behavior and coined the term *synapse* to describe the junction between two neurons. With Golgi, Ramón y Cajal, and these other bright minds, the neuron doctrine was born—a discovery whose importance was highlighted by two Nobel Prizes in Physiology or Medicine: the 1906 prize shared by Golgi and Ramón y Cajal, and the 1932 prize awarded to Sherrington along with his colleague Edgar Adrian.

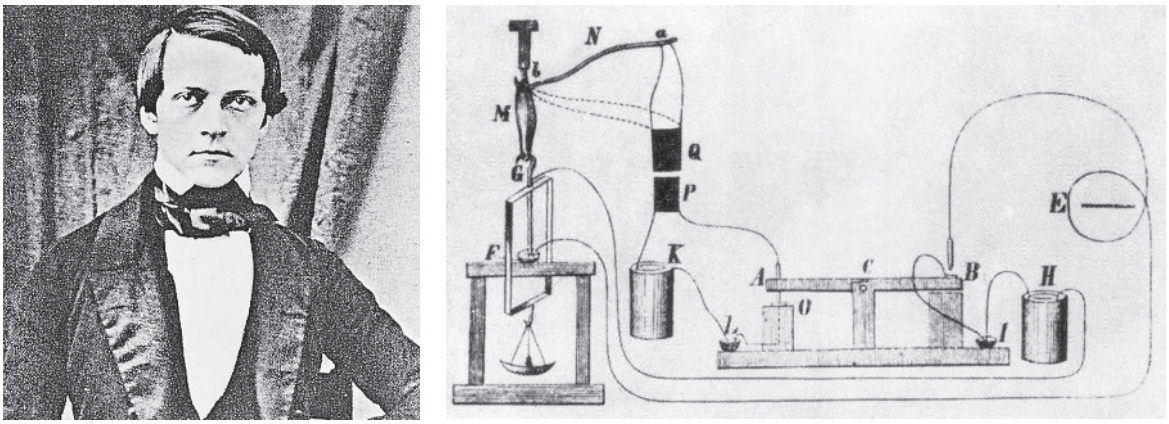


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b

FIGURE 1.14
(a) Jan Evangelista Purkinje (1787–1869), who described the first nerve cell in the nervous system. **(b)** A Purkinje cell of the cerebellum.



a b

FIGURE 1.15
(a) Hermann Ludwig von Helmholtz (1821–1894). (b) Helmholtz's apparatus for measuring the velocity of neuronal conduction.

As the 20th century progressed, the localizationist views were mediated by those who saw that, even though particular neuronal locations might serve independent functions, the network of these locations and the interactions between them are what yield the integrated, holistic behavior that humans exhibit. Once again, this neglected idea had previously been discussed nearly a century earlier, this time by the French biologist Claude Bernard, who wrote in 1865,

> If it is possible to dissect all the parts of the body, to isolate them in order to study them in their structure, form and connections it is not the same in life, where all parts cooperate at the same time in a common aim. An organ does not live on its own, one could often say it did not exist anatomically, as the boundary established is sometimes purely arbitrary. What lives, what exists, is the whole, and if one studies all the parts of any mechanisms separately, one does not know the way they work. (Bernard, 1865/1957, quoted in Finger, 1994, p. 57)

Thus, scientists have come to believe that the knowledge of the parts (the neurons and brain structures) must be understood in conjunction with the whole (i.e., what the parts make when they come together: the mind). Next we explore the history of research on the mind.

1.3 The Psychological Story

Physicians were the early pioneers studying how the brain worked. In 1868 a Dutch ophthalmologist, Franciscus Donders, was the first to propose the now common method of using differences in reaction times to infer differences in cognitive processing (Donders, 1868/1969). He suggested that the difference between the amount of time it took to react to a light and the amount of time needed to react to a particular color of light was the amount of time required for the process of identifying a color. Psychologists began to use this approach, claiming that they could study the mind by measuring behavior, and experimental psychology was born.

Before the start of experimental psychological science, the mind had been the province of philosophers who wondered about the nature of knowledge and how we come to know things. The philosophers had two main positions: **rationalism** and **empiricism**. Rationalism grew out of the Enlightenment period and held that all knowledge could be gained through the use of reason alone: Truth was intellectual, not sensory. Through thinking, then, rationalists would determine true beliefs and would reject beliefs that, although perhaps comforting, were unsupportable and even superstitious. Among intellectuals and scientists, rationalism replaced religion and became the only way to think about the world. In particular, this view, in one form or another, was supported by René Descartes, Baruch Spinoza, and Gottfried Leibniz.

Although rationalism is frequently equated with logical thinking, the two are not identical. Rationalism considers such issues as the meaning of life, whereas logic does not. Logic relies simply on inductive reasoning, statistics, probabilities, and the like. It does not concern itself with personal mental states like happiness, self-interest, and public good. Each person weighs these issues differently, and as a consequence, a rational decision is more problematic than a simple logical decision.

Empiricism, by contrast, is the idea that all knowledge comes from sensory experience, that the brain begins life

as a blank slate. Direct sensory experience produces simple ideas and concepts. When simple ideas interact and become *associated* with one another, complex ideas and concepts are created in an individual's knowledge system. The British philosophers—from Thomas Hobbes in the 17th century, through John Locke and David Hume, to John Stuart Mill in the 19th century—all emphasized the role of experience. It is no surprise, then, that a major school of experimental psychology arose from this associationist view. Psychological associationists believed that the aggregate of a person's experience determined the course of mental development.

One of the first scientists to study **associationism** was the German psychologist Hermann Ebbinghaus, who, in the late 1800s, decided that complex processes like memory could be measured and analyzed. He took his lead from the great psychophysicists Gustav Fechner and Ernst Heinrich Weber, who were hard at work relating the physical properties of things such as light and sound to the psychological experiences that they produce in the observer. These measurements were rigorous and reproducible. Ebbinghaus was one of the first to understand that mental processes that are more internal, such as memory, also could be measured (see Chapter 9).

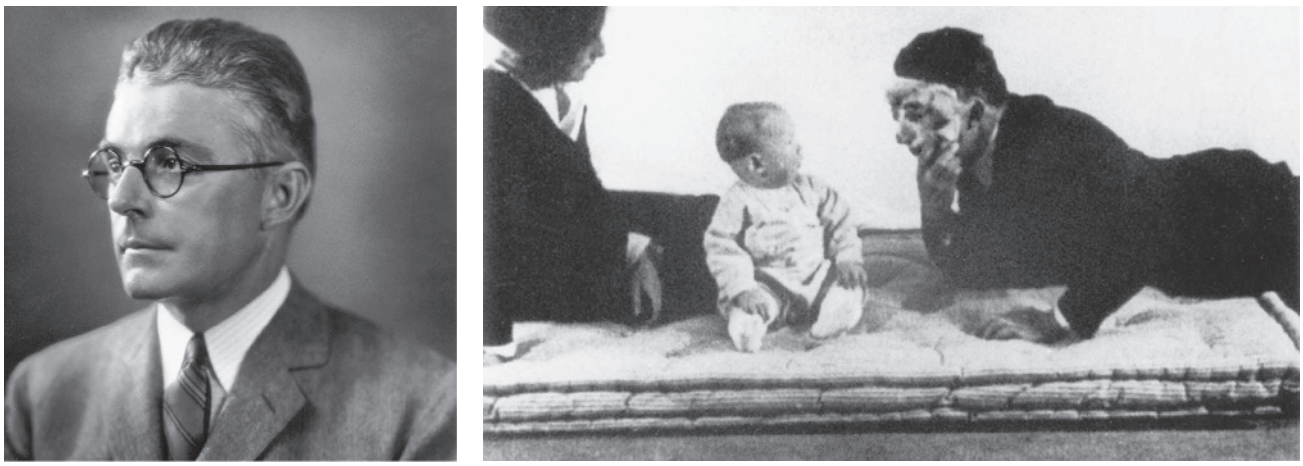
Even more influential to the shaping of the associationist view was a 1911 monograph by the American psychologist Edward Thorndike (**Figure 1.16**). In it, he described his observations that a response that was followed by a reward would be stamped into the organism as a habitual response. If no reward followed a response, the response would disappear. Thus, rewards provided a mechanism for establishing a more adaptive response.



FIGURE 1.16
Edward L. Thorndike (1874–1949).

Associationism became the psychological explanation for behavior, and soon the American behavioral psychologist John B. Watson (**Figure 1.17**) dominated the field. He proposed that psychology could be objective only if it was based on observable behavior. He rejected Ebbinghaus's methods and declared that all talk of mental processes, which cannot be publicly observed, should be avoided. These ideas evolved into the methodological stance of **behaviorism**.

Behaviorism became committed to an idea, widely popularized by Watson, that he could turn any baby into an adult that could do anything from tightrope walking to neurosurgery. Learning was the key, he proclaimed, and everybody had the same neural equipment on which learning could build. Appealing to the American sense of equality, American psychology was giddy with this idea of the brain as a *blank slate* upon which to build through learning and experience. Though disciples of the blank slate and behaviorism were well-intentioned, a behaviorist–associationist bias had crept in, and every prominent psychology department in the country was run by people who held this view. Behaviorism persisted despite the already well-established position—first articulated by Descartes, Leibniz, Immanuel Kant, Charles Darwin, and others—that complexity is built into the human organism. Sensory



a b

FIGURE 1.17
(a) John B. Watson (1878–1958). **(b)** Watson and "Little Albert," the focus of study in one of Watson's fear-conditioning experiments.

information is merely data on which preexisting mental structures act. This idea, which dominates psychology today, was blithely asserted in that golden age, and later forgotten or ignored.

Psychologists in Britain and Canada did not share the behaviorist bias, however, and Montreal became a hot spot for new ideas on how biology shapes cognition and behavior. In 1928 Wilder Penfield (**Figure 1.18**), an American who had studied neuropathology with Sherrington at Oxford, became that city's first neurosurgeon. In collaboration with Herbert Jasper, Penfield invented the **Montreal procedure** for treating epilepsy, in which he surgically destroyed the neurons in the brain that produced the seizures. To determine which cells to destroy, he stimulated various parts of the brain with electrical probes and observed the results on the patients—who were awake, lying on the operating table under local anesthesia only. From these observations, he was able to create maps of the sensory and motor cortices in the brain (Penfield & Jasper, 1954), confirming the topographic predictions of John Hughlings Jackson from over half a century earlier.

Penfield was joined by a Nova Scotian psychologist, Donald Hebb (**Figure 1.19**), to study the effects of brain surgery and injury on the functioning of the brain. Hebb became convinced that the workings of the brain explained behavior, and that the psychology and biology of an organism could not be separated. Although this idea—which has kept popping up, only to be swept under the carpet again and again, over the past few hundred years—is well accepted now, Hebb was a maverick at the time.

In 1949 he published a book, *The Organization of Behavior: A Neuropsychological Theory*, that rocked the psychological world. In it he postulated that learning had a biological basis. The well-known neuroscience mantra "cells that fire together, wire together" is a distillation of his proposal that neurons can combine together into a single processing unit, and that the connection patterns of these units make up the ever-changing algorithms that determine the brain's response to a stimulus. He pointed out that the brain is active all the time, not just when stimulated by an impulse, and that inputs from the outside can only modify the ongoing activity. Hebb's theory was subsequently used in the design of artificial neural networks.

Hebb's British graduate student Brenda Milner (**Figure 1.20**) continued the behavioral studies on Penfield's patients, both before and after their surgery. When postsurgical patients began to complain about mild memory loss, Milner became interested and was the first to provide anatomical and physiological proof that there are multiple memory systems. Brenda Milner is one of the earliest in a long line of influential women in the field.

The true end of the dominance of behaviorism and stimulus–response psychology in the United States did not come until the late 1950s, when psychologists began to think in terms of cognition, not just behavior. George Miller (**Figure 1.21**), who had been a confirmed behaviorist, had a change of heart in the 1950s. In 1951 he had written an influential book entitled *Language and Communication* and noted in the preface, "The bias is behavioristic." Eleven years later, in 1962, he wrote another book, called *Psychology, the Science of Mental Life*—a title signaling a complete rejection of the idea that psychology should study only behavior.

Upon reflection, Miller determined that the exact date of his rejection of behaviorism and his cognitive awakening was September 11, 1956, during the second Symposium on Information Theory, held at the Massachusetts Institute of Technology (MIT). That year had been a rich one for several disciplines. In computer science, Allen Newell and Herbert Simon successfully introduced Information Processing Language I, a powerful program that simulated the proof of logic theorems.



FIGURE 1.18
Wilder Penfield (1891–1976).

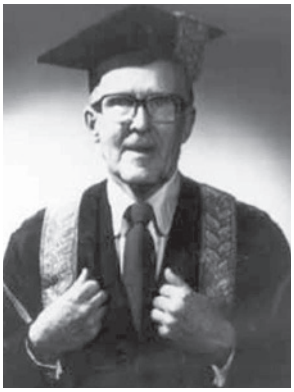


FIGURE 1.19
Donald O. Hebb (1904–1985).



FIGURE 1.20
Brenda Milner (1918–).

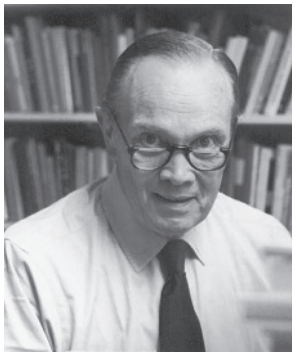


FIGURE 1.21
George A. Miller (1920–2012).

The computer guru John von Neumann wrote the Silliman lectures on neural organization, in which he considered the possibility that the brain's computational activities were similar to a massively parallel computer. A famous meeting on artificial intelligence was held at Dartmouth College, where Marvin Minsky, Claude Shannon (known as the father of information theory), and many others were in attendance.

Big things were also happening in psychology. Signal detection and computer techniques, developed in World War II to help the U.S. Department of Defense detect submarines, were now being applied by psychologists James Tanner and John Swets to study perception. In 1956 Miller published his classic and entertaining paper "The Magical Number Seven, Plus-or-Minus Two," in which he described an experiment revealing a limit to the amount of information we can keep in short-term memory: about seven items. Miller concluded that the brain, among other things, is an information processor and, breaking the bonds of behaviorism, he realized that the contents of the mind could be studied, setting into motion the "cognitive revolution."

That same year, Miller also came across a preliminary version of the linguist Noam Chomsky's ideas on syntactic theories (**Figure 1.22**; for a review, see Chomsky, 2006). In an article titled "Three Models for the Description of Language," Chomsky showed how the sequential predictability of speech follows from adherence to grammatical, not probabilistic, rules. For example, while children are exposed to only a finite set of word orders, they can come up with a sentence and word order that they have never heard before. They did not assemble that new sentence using associations made from previous exposure to word orders. Chomsky's deep message, which Miller gleaned, was that learning theory—that is, associationism, then heavily championed by the behaviorist B. F. Skinner—could *in no way* explain how children learned language. The complexity of language was built into the brain, and it ran on rules and principles that transcended all people and all languages. It was innate and it was universal.

Thus, on September 11, 1956, after a year of great development and theory shifting, Miller realized that, although behaviorism had important theories to offer, it could not explain all learning. He then set out with Chomsky to understand the psychological implications of Chomsky's theories by using psychological testing methods, and the field of cognitive psychology was born. Miller's ultimate goal was to understand how the brain works as an integrated whole—to understand the workings of the brain *and* the conscious mind it produces. Many followed his mission, and a few years later a new field was born: cognitive neuroscience.



FIGURE 1.22
Noam Chomsky (1928–).



FIGURE 1.23
Patricia Goldman-Rakic (1937–2003).

What has come to be a hallmark of cognitive neuroscience is that it is made up of an *insalata mista* ("mixed salad") of different disciplines. Miller had stuck his nose into the worlds of linguistics and computer science and had come out with revelations for psychology and neuroscience. In the same vein, in the 1970s Patricia Goldman-Rakic (**Figure 1.23**) put together a multidisciplinary team of people working in biochemistry, anatomy, electrophysiology, pharmacology, and behavior. She was curious about one of Brenda Milner's memory systems, working memory, and chose to ignore the behaviorists' claim that the higher cognitive function of the prefrontal cortex could not be studied. As a result, she produced the first description of the circuitry of the prefrontal cortex and how it relates to working memory (Goldman-Rakic, 1987).

Later, Goldman-Rakic discovered that individual cells in the prefrontal cortex are dedicated to specific memory tasks, such as remembering a face or a voice. She also performed the first studies on the influence of dopamine on the prefrontal cortex. Her findings caused a phase shift in the understanding of many mental illnesses—including schizophrenia, which previously had been thought to be the result of bad parenting.

1.4 The Instruments of Neuroscience

Changes in electrical impulses, fluctuations in blood flow, and shifts in utilization of oxygen and glucose are the driving forces of the brain's business. They are also the parameters that are measured and analyzed in the various methods used to study how mental activities are supported by brain functions. The advances in technology and the invention of these methods have provided cognitive neuroscientists the tools to study how the brain enables the

mind. Without these instruments, the discoveries made in the past 30 years would not have been possible. In this section we provide a brief history of the people, ideas, and inventions behind some of the noninvasive techniques used in cognitive neuroscience. Many of these methods are discussed in greater detail in Chapter 3.

Electroencephalography

In 1875, shortly after Hermann von Helmholtz figured out that it was actually an electrical impulse wave that carried messages along the axon of a nerve, British physician Richard Caton used a galvanometer to measure continuous spontaneous electrical activity from the cerebral cortex and skull surface of live dogs and apes. A fancier version, the "string galvanometer," designed by a Dutch physician, Willem Einthoven, was able to make photographic recordings of the electrical activity. Using this apparatus, the German psychiatrist Hans Berger published a paper describing recordings of a human brain's electrical currents in 1929. He named the type of recording an electroencephalogram. The method for making the recordings, electroencephalography, remained the sole technique for noninvasive brain study for a number of years.

Measuring Blood Flow in the Brain

Angelo Mosso, a 19th-century Italian physiologist, was interested in blood flow in the brain and studied patients who had skull defects as a result of neurosurgery. He recorded pulsations as blood flowed around and through the cortex in these patients (**Figure 1.24**) and noticed that the pulsations of the brain increased locally during mental activities such as mathematical calculations. He inferred that blood flow followed function.

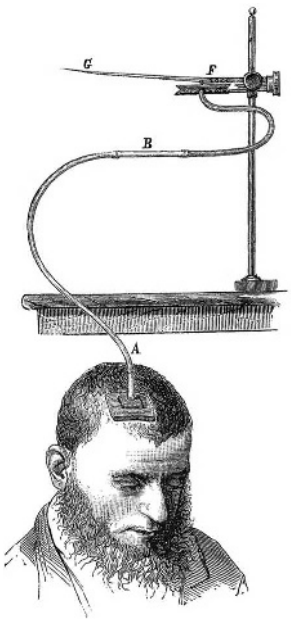


FIGURE 1.24
Angelo Mosso's experimental setup was used to measure pulsations of the brain at the site of a skull defect.

These observations slipped from view and were not pursued until 1928, when the neurophysiologist and physician John Fulton presented the case of patient Walter K., who was evaluated for a vascular malformation that resided above his visual cortex (**Figure 1.25**). The patient mentioned that he heard a noise at the back of his head that increased when he used his eyes but not his other senses. This noise was a bruit, the sound that blood makes when it rushes through a narrowing of its channel. Fulton concluded that blood flow to the visual cortex varied with the attention paid to surrounding objects.

Another 20 years slipped by before Seymour Kety (**Figure 1.26**), a young physician at the University of Pennsylvania, realized that if you could perfuse arterial blood with an inert gas, such as nitrous oxide, then the gas would circulate through the brain and be absorbed independently of the brain's metabolic activity. Its accumulation would depend only on measurable physical parameters such as diffusion, solubility, and perfusion.

With this idea in mind, he developed a method to measure the blood flow and metabolism of the human brain as a whole and, using more drastic methods in animals (they were decapitated, and their brains then removed and analyzed), was able to measure the blood flow to specific regions of the brain (Landau et al., 1955). His animal studies provided evidence that blood flow was related directly to brain function. Kety's method and results were used in developing positron emission tomography (described later in this section), which uses radioactive tracers rather than an inert gas.

Computerized Axial Tomography

Although blood flow was of interest to those studying brain function, having good anatomical images that could pinpoint the location of tumors was motivating other developments in instrumentation. Investigators needed to be able to obtain three-dimensional views of the inside of the human body. In the 1930s, the Italian radiologist Alessandro Vallebona developed tomographic



FIGURE 1.25
Walter K.'s head, showing the skull defect over the occipital cortex.



FIGURE 1.26
Seymour S. Kety (1915–2000).

radiography, a technique in which a series of transverse sections are taken. Improving on these initial attempts, UCLA neurologist William Oldendorf (1961) wrote an article providing the first description of the basic concept that was later used in computerized tomography (CT), in which a series of transverse X-rays could be reconstructed into a three-dimensional picture.

Oldendorf's concept was revolutionary, but he could not find any manufacturers willing to capitalize on his idea. It took insight and cash, which were provided by four lads from Liverpool, the company EMI, and Godfrey Newbold Hounsfield, a computer engineer who worked at the Central Research Laboratories of EMI, Ltd. EMI was an electronics firm that also owned Capitol Records and the Beatles' recording contract. Hounsfield, using mathematical techniques and multiple two-dimensional X-rays to reconstruct a three-dimensional image, developed his first scanner, and as the story goes, EMI, flush with cash from the Beatles' success, footed the bill. Hounsfield performed the first computerized axial tomography (CAT) scan in 1972. (Note that the terms *computerized tomography*, or CT, and *computerized axial tomography*, CAT, are equivalent.)

Positron Emission Tomography and Radioactive Tracers

While CAT was great for revealing anatomical detail, it revealed little about function. Researchers at Washington University, however, used CAT as the basis for developing positron emission tomography (PET), a noninvasive sectioning technique that could provide information about function. Observations and research by a huge number of people over many years have been incorporated into what ultimately is today's PET.

The development of PET is interwoven with that of the radioactive isotopes, or "tracers," that it employs. In 1934 the French scientist Irène Joliot-Curie (**Figure 1.27**) and her husband, Frédéric Joliot-Curie, discovered that some originally nonradioactive nuclides emitted penetrating radiation after being irradiated. This observation led Ernest O. Lawrence (the inventor of the cyclotron) and his colleagues at UC Berkeley to realize that the cyclotron could be used to produce radioactive substances. If radioactive forms of oxygen, nitrogen, or carbon could be produced, then they could be injected into the blood circulation and would become incorporated into biologically active molecules. These molecules would concentrate in an organ, where the radioactivity would begin to decay. The concentration of the tracers could then be measured over time, allowing inferences about metabolism.



FIGURE 1.27
Irène Joliot-Curie (1897–1956).

In 1950, Gordon Brownell at Harvard University realized that positron decay (of a radioactive tracer) was associated with two gamma particles being emitted 180° apart. This handy discovery made possible the design and construction of a simple positron scanner with a pair of sodium iodide detectors. The machine was scanning patients for brain tumors in a matter of months (Sweet & Brownell, 1953). In 1959 David E. Kuhl, a radiology resident at the University of Pennsylvania who had been dabbling with radiation since high school (did his parents know?), and Roy Edwards, an engineer, combined tomography with gamma-emitting radioisotopes and obtained the first emission tomographic image.

The problem with most radioactive isotopes of nitrogen, oxygen, carbon, and fluorine is that their half-lives are measured in minutes. Anyone who was going to use them had to have their own cyclotron and be ready to roll as the isotopes were created. It happened that Washington University had both a cyclotron that produced radioactive oxygen-15 (^{15}O) and two researchers, Michel Ter-Pogossian and William Powers, who were interested in using it. They found that when injected into the bloodstream, ^{15}O-labeled water could be used to measure blood flow in the brain (Ter-Pogossian & Powers, 1958).

Ter-Pogossian (**Figure 1.28**) was joined in the 1970s by Michael Phelps (**Figure 1.29**), a graduate student who had started out his career as a Golden Gloves boxer. Excited about X-ray CT, they thought that they could adapt the technique to reconstruct the distribution within

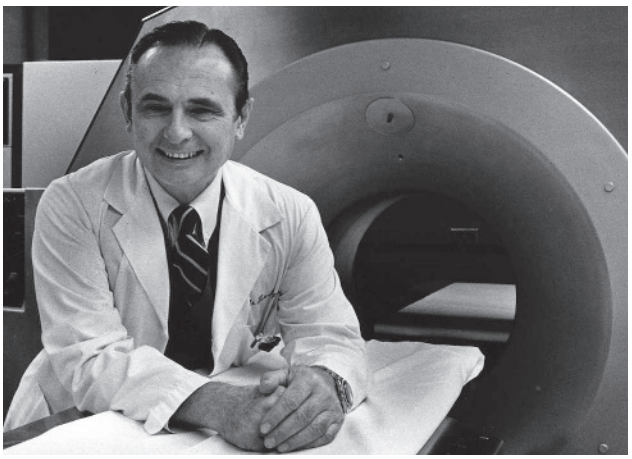


FIGURE 1.28
Michel M. Ter-Pogossian (1925–1996).



FIGURE 1.29
Michael E. Phelps (1939–).

an organ of a short-lived "physiological" radionuclide from its emissions. They designed and constructed the first positron emission tomograph and dubbed the method PETT (positron emission transaxial tomography; Ter-Pogossian et al., 1975), which later was shortened to PET.

Another metabolically important molecule in the brain is glucose. Under the direction of Joanna Fowler and Al Wolf, using Brookhaven National Laboratory's powerful cyclotron, ^{18}F-labeled 2-fluorodeoxy-D-glucose (2FDG) was created (Ido et al., 1978). Fluorine-18 has a half-life that is amenable to use in PET imaging and can give precise values of energy metabolism in the brain. The first work using PET to look for neural correlates of human behavior began when Phelps and Kuhl got together. Using 2FDG, they established a method for imaging the tissue consumption of glucose. Phelps, in a leap of insight, invented the block detector, a device that eventually increased spatial resolution of PET from 3 cm to 3 mm.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is based on the principle of nuclear magnetic resonance, which was first described and measured by the physicist Isidor Rabi in 1938. Discoveries made independently in 1946 by physicists Felix Bloch at Harvard University and Edward Purcell at Stanford University expanded the understanding of nuclear magnetic resonance to liquids and solids. For example, the protons in a water molecule line up like little bar magnets when placed in a magnetic field. If the equilibrium of these protons is disturbed by being zapped with radio frequency pulses, then a measurable voltage is induced in a receiver coil. The voltage changes over time as a function of the proton's environment. Analysis of the voltages can yield information about the examined tissue.

While on sabbatical in 1971, the chemist Paul Lauterbur (**Figure 1.30**) was thinking grand thoughts as he ate a fast-food hamburger. He scribbled his ideas on a nearby napkin, and from these humble beginnings he developed the theoretical model that led to the invention of the first magnetic resonance imaging scanner, located at SUNY Stony Brook (Lauterbur, 1973). It was another 20 years, however, before MRI was used to investigate brain function.

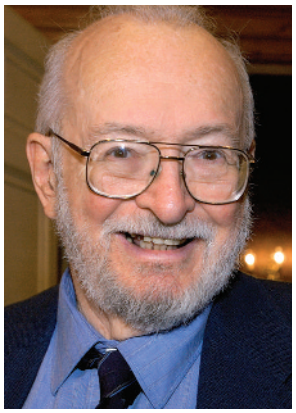


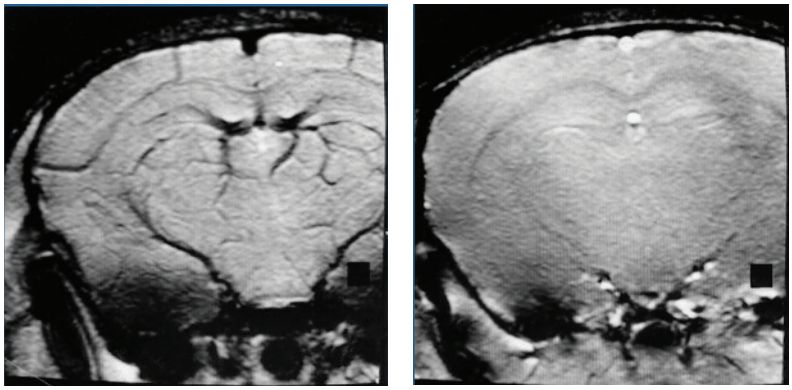
FIGURE 1.30
Paul Lauterbur (1929–2007).

In the early 1990s, researchers at Massachusetts General Hospital demonstrated that after contrast material was injected into the bloodstream, changes in the blood volume of a human brain, produced by physiological manipulation of blood flow, could be measured using MRI (Belliveau et al., 1990). Not only were excellent anatomical images produced, but they could be linked to physiology that was germane to brain function. Lauterbur ultimately won the 2003 Nobel Prize in Physiology or Medicine for developing the theory behind MRI, though his first attempt at publishing his findings had been rejected by the journal *Nature.* He later quipped, "You could write the entire history of science in the last 50 years in terms of papers rejected by *Science* or *Nature*" (Wade, 2003).

Functional Magnetic Resonance Imaging

When PET was introduced, the conventional wisdom was that increased blood flow to differentially active parts of the brain was driven by the brain's need for more oxygen. An increase in oxygen delivery permitted more glucose to be metabolized, and thus more energy would be available for performing the task. Although this idea sounded reasonable, few data were available to back it up. In fact, if this proposal were true, then increases in blood flow induced by functional demands should be similar to the increase in oxygen consumption. This would mean that the ratio of oxygenated to deoxygenated hemoglobin should stay constant. PET data, however, did not back up the hypothesis (Raichle, 2008).

Instead, Peter Fox and Marc Raichle, at Washington University, found that although functional activity induced increases in blood flow, there was no corresponding increase in oxygen consumption (Fox & Raichle, 1986). In addition, more glucose was being used than would be predicted from the amount of oxygen consumed (Fox et al., 1988). What was up with that? Raichle (2008) relates that, oddly enough, a random scribble written in the margin of Michael Faraday's lab notes in 1845 (Faraday, 1933) provided the hint that led to the solution of this puzzle. It was Linus Pauling and Charles Coryell who somehow happened upon this clue.



a Air **b** O_2

FIGURE 1.31
Images of a mouse brain under varying oxygen conditions: (a) air; (b) O_2.

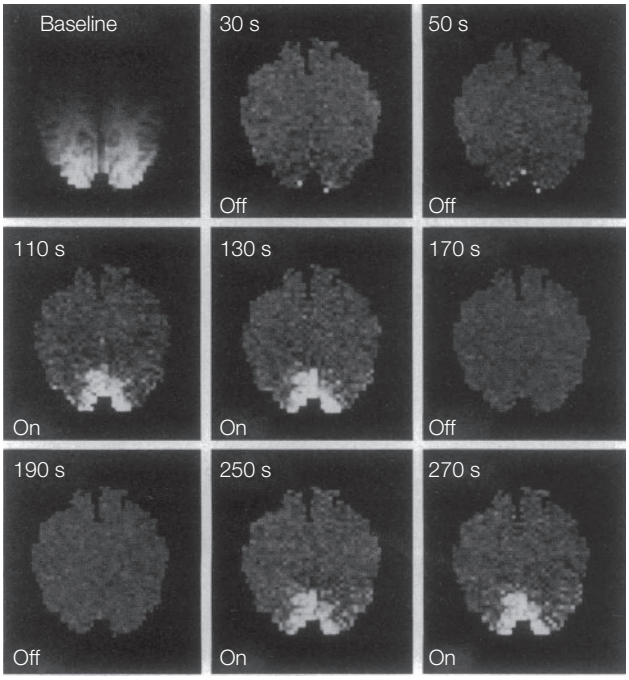
Faraday had noted that dried blood was not magnetic, and in the margin of his notes he had written that he must try fluid blood. He was puzzled because hemoglobin contains iron, a typically magnetic element. Ninety years later, Pauling and Coryell (1936), after reading Faraday's notes, became curious too. They found that, indeed, oxygenated and deoxygenated hemoglobin behave very differently in a magnetic field. Deoxygenated hemoglobin is weakly magnetic because of the exposed iron in the hemoglobin molecule.

Years later, Keith Thulborn remembered and capitalized on this property described by Pauling and Coryell, realizing that it was feasible to measure the state of oxygenation in vivo (Thulborn et al., 1982). Seiji Ogawa (1990) and his colleagues at AT&T Bell Laboratories tried manipulating oxygen levels by administering 100% oxygen alternated with room air (21% oxygen) to human subjects who were undergoing MRI. They discovered that on room air, the structure of the venous system was visible because of the contrast provided by the deoxygenated hemoglobin that was present. On 100% O_2, however, the venous system completely disappeared (**Figure 1.31**). Thus, contrast depended on the blood oxygen level. BOLD (blood oxygen level–dependent) contrast was born.

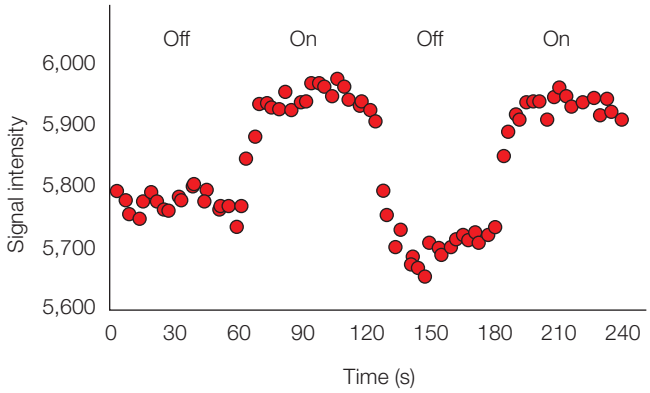
This technique led to the development of functional magnetic resonance imaging (fMRI). Functional MRI does not use ionizing radiation, it combines beautifully detailed images of the body with physiology related to brain function, and it is sensitive. Ken Kwong (a nuclear medicine physicist at Mass General) and his colleagues published the first human fMRI scans in 1992 (**Figure 1.32**). With all of these advantages, it did not take long for MRI and fMRI to be adopted by the research community, resulting in explosive growth of functional brain imaging.

Machines are useful only if you know what to do with them and what their limitations are. Raichle understood the potential of these new scanning methods, but he also realized that some basic problems had to be solved. If generalized information about brain function and anatomy were to be obtained, then the scans from different individuals performing the same tasks under the same circumstances had to be comparable. Achieving comparable results was proving difficult, however, since no two brains are precisely the same size and shape. Furthermore, early data were a mishmash of results that varied in anatomical location from person to person. Eric Reiman, a psychiatrist working with Raichle, suggested that averaging blood flow across subjects might solve this problem. The results of this approach were unambiguous, and the landmark paper that followed (Fox et al., 1988) presented the first integrated approach for the design, execution, and interpretation of functional brain images.

What really can be learned about the brain and the behavior of a human when a person is lying prone in a scanner? Cognitive psychologists Michael Posner, Steve Petersen, and Gordon Shulman, at Washington University, had developed innovative experimental paradigms including the cognitive subtraction method (first proposed by Franciscus Donders) for use while scanning with PET. The methodology was soon applied to fMRI. This joining together of cognitive psychology's experimental methods with brain imaging was the beginning of human functional brain mapping. Throughout this book, we will draw from the wealth of brain-imaging data that has been amassed in the last 40 years in our quest to learn about how the brain enables the mind.



a fMRI images



b MRI visual cortex response

FIGURE 1.32 The first set of images from fMRI done on humans. **(a)** Activation of the V1 region of visual cortex. **(b)** MRI visual cortex response. Signal intensity increases for a region of interest within the visual cortex when a light is off and then switched on. When the light is then turned off again, an undershoot in signal intensity occurs, consistent with known physiological oxygenation and pH changes.

1.5 The Book in Your Hands

Our goals in this book are to introduce you to the big questions and discussions in cognitive neuroscience and to teach you how to think, ask questions, and approach those questions like a cognitive neuroscientist. In the next chapter we introduce the biological foundations of the brain by presenting an overview of its cellular mechanisms and neuroanatomy. In Chapter 3 we discuss the methods that are available to us for observing mind–brain relationships, and we introduce how scientists go about interpreting and questioning those observations. Building on this foundation, in Chapters 4 through 11 we launch into the core processes of cognition: hemispheric specialization, sensation and perception, object recognition, attention, the control of action, learning and memory, emotion, and language, devoting a chapter to each. These are followed by chapters on cognitive control, social cognition, and consciousness.

Each chapter begins with a story that illustrates and introduces the chapter's main topic. Beginning with Chapter 4, the story is followed by an anatomical orientation highlighting the portions of the brain that we know are involved in these processes. Next, the heart of the chapter focuses on a discussion of the cognitive process and what is known about how it functions, followed by a summary and suggestions for further reading for those whose curiosity has been aroused.

Summary

Thomas Willis first introduced us, in the mid 1600s, to the idea that damage to the brain could influence behavior and that the cerebral cortex might indeed be the seat of what makes us human. Phrenologists expanded on this idea and developed a localizationist view of the brain. Patients like those of Broca and Wernicke later supported the importance of specific brain locations on human behavior (like language). Ramón y Cajal, Sherrington, and Brodmann, among others, provided evidence that although the microarchitecture of distinct brain regions could support a localizationist view of the brain, these areas are interconnected. Soon, scientists began to realize that the integration of the brain's neural networks might be what enables the mind.

At the same time that neuroscientists were researching the brain, psychologists were studying the mind, with its thoughts, beliefs, intentions, and so forth. Out of the philosophical theory of empiricism came the idea of associationism: that any response followed by a reward would be maintained, and that these associations were the basis of how the mind learned. Associationism was the prevailing theory for many years, until Hebb emphasized the biological basis of learning, and Chomsky and Miller realized that associationism couldn't explain all learning or all actions of the mind.

Neuroscientists and psychologists both reached the conclusion that there is more to the brain than just the sum of its parts, that the brain must enable the mind—but how? The term *cognitive neuroscience* was coined in the late 1970s because the fields of neuroscience and psychology were once again coming together. Neuroscience was in need of the theories of the psychology of the mind, and psychology was ready for a greater understanding of the working of the brain. The resulting marriage is cognitive neuroscience.

The last half of the 20th century saw a blossoming of interdisciplinary research that produced both new approaches and new technologies resulting in noninvasive methods for imaging brain structure, metabolism, and function.

So, welcome to cognitive neuroscience! It doesn't matter what your background is; there's a place for you here.

Key Terms

aggregate field theory (p. 7)
associationism (p. 12)
behaviorism (p. 12)
cognitive neuroscience (p. 4)
cytoarchitectonics (p. 9)
empiricism (p. 11)
Montreal procedure (p. 13)
neuron doctrine (p. 10)
phrenology (p. 6)
rationalism (p. 11)
syncytium (p. 10)

Think About It

1. Can we study how the mind works without studying the brain?
2. Will modern brain-imaging experiments become the new phrenology?
3. How do you think the brain might be studied in the future?
4. Why do good ideas and theories occasionally get lost over the passage of time? How do they often get rediscovered?

Suggested Reading

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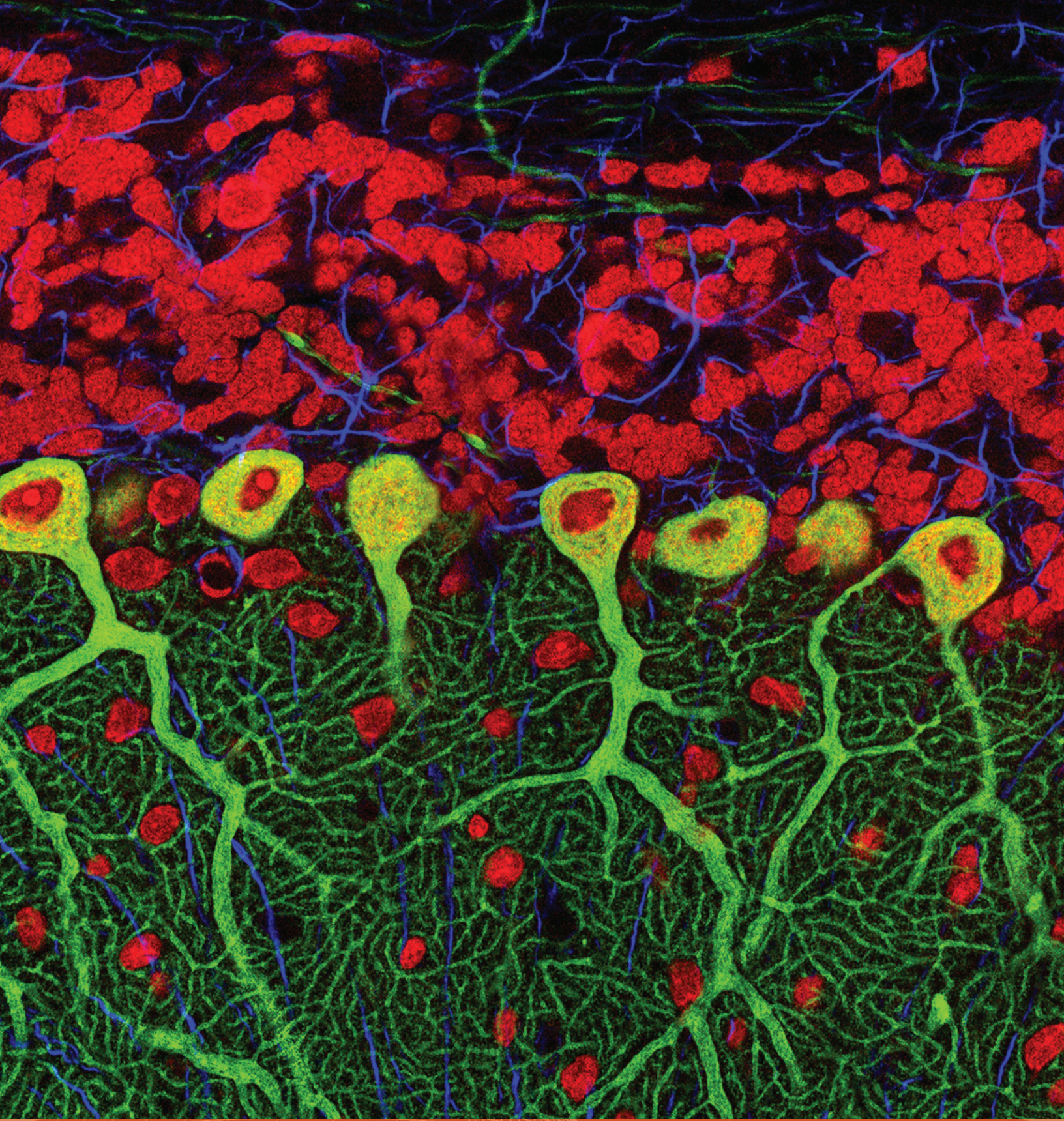
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You shake my nerves and you rattle my brain.

Jerry Lee Lewis

CHAPTER

2

Structure and Function of the Nervous System

ONE DAY IN 1963, neuroscientist Jose Delgado coolly stood in a bullring in Córdoba, Spain, facing a charging bull. He did not sport the Spanish matador's typical gear of toreador pants, jacket, and sword, however. Instead, he stepped into the ring in slacks and a pullover sweater—and, for effect, a matador's cape—while holding a small electronic device in his hand. He was about to see if it worked.

The bull turned and charged, but Delgado stood his ground, his finger on the device's button. Then he pushed it. The bull skidded to a stop, standing a few feet before the scientist (**Figure 2.1**). The now placid bull stood there looking at Delgado, who gazed back, smiling. This otherwise ordinary bull had one odd feature that gave Delgado confidence: a surgically implanted electric stimulator in its caudate nucleus. The device in Delgado's hand was a radio transmitter that he had built to activate the stimulator. By stimulating the bull's caudate nucleus, Delgado had turned off its aggression.

What motivated Delgado's unusual scientific experiment? Years before, Delgado had been horrified by the increasingly popular frontal lobotomy surgical procedure that destroyed brain tissue—and along with it, its function—in order to treat mental disorders. He was interested in finding a more conservative approach to treating these disorders through electrical stimulation. Using his knowledge of the electrical properties of neurons, neuroanatomy, and brain function, Delgado designed the first remote-controlled neural implants ever to be used. Exceedingly controversial at the time, they were the forerunners of the now common intracranial devices that are used for stimulating the brain to treat disorders such as Parkinson's disease, chronic pain, neuromuscular dysfunction, and other maladies.

Delgado understood that the nervous system uses electrochemical signaling for communication. He also understood that inside the brain, neurons and their long-distance projections (axons) form intricate wiring patterns. An electrical signal

BIG Questions

- What are the elementary building blocks of the brain?
- How is information coded and transmitted in the brain?
- What are the organizing principles of the brain?
- What does the brain's structure tell us about its function and the behaviors it supports?



FIGURE 2.1 Jose Delgado halting a charging bull by remote control.

initiated at one location can travel to another location to trigger the contraction of a muscle, or the initiation or cessation of a behavior. This knowledge is the foundation on which all theories of neuronal signaling are built.

Our goal as cognitive neuroscientists is to figure out what the 89 billion neurons of the human brain do and how their collective action enables us to walk, talk, and imagine the unimaginable. We can approach the biological system that is the brain from several levels of analysis: from atomic, molecular, and cellular levels upward to circuit, network, system, and cognitive levels, and finally, to the highest levels, involving the interactions of humans with each other—our familial, societal, and cultural lives.

Since all theories of how the brain enables the mind must ultimately mesh with the actual nuts and bolts of the nervous system, and what it can and cannot do, we need to understand the basics of neurons. We must appreciate the structure and function of neurons on the individual level, as well as when they are strung together into the circuits, networks, and systems that form the brain and the nervous system as a whole. Thus, for us, it is important to understand the basic physiology of neurons and the anatomy of the nervous system. In this chapter we review the principles of brain structure that support cognition. In chapters that follow, we look at what results from the activity within and among specific brain circuits, networks, and systems (e.g., perception, cognition, emotion, and action).

2.1 The Cells of the Nervous System

The nervous system is composed of two main classes of cells: neurons and glial cells. **Neurons** are the basic signaling units that transmit information throughout the nervous system. As Santiago Ramón y Cajal and others of his time deduced, neurons take in information, make a "decision" about it following some relatively simple rules, and then, by changes in their activity levels, pass the signal along to other neurons or muscles. Neurons vary in their form, location, and interconnectivity within the nervous system (**Figure 2.2**), and these variations are closely related to their functions. **Glial cells** serve various functions in the nervous system, providing structural support and electrical insulation to neurons and modulating neuronal activity. We begin with a quick look at glial cells, after which we will turn our focus back to neurons.

Glial Cells

There are roughly as many glial cells in the brain as there are neurons. The central nervous system has three main types of glial cells: astrocytes, microglial cells, and oligodendrocytes (**Figure 2.3**). *Astrocytes* are large glial cells with round or radially symmetrical forms; they surround neurons and are in close contact with the brain's vasculature. An astrocyte makes contact with blood vessels at specializations called end feet, which permit the astrocyte to transport ions across the vascular wall.

The astrocytes create a barrier, called the **blood–brain barrier (BBB)**, between the tissues of the central nervous system and the blood. The BBB restricts the diffusion of microscopic objects (such as most bacteria) and large hydrophilic molecules in the blood from entering the neural tissue, but it allows the diffusion of small hydrophobic molecules, such as oxygen, carbon dioxide, and hormones. Many drugs and certain neuroactive agents, including dopamine and norepinephrine, when placed in the blood, cannot cross the BBB. Thus, it plays a vital role in protecting the central nervous system from blood-borne agents such as chemical compounds and also pathogens.

Evidence gathered over the past decade suggests that astrocytes also have an active role in brain function. In vitro studies indicate that they respond to and release neurotransmitters and other neuroactive substances that affect neuronal activity and modulate synaptic strength. In vivo studies found that when astrocyte activity is blocked, neuronal activity increases, supporting the notion that neuronal activity is moderated by astrocyte activity (Schummers et al., 2008). It is hypothesized that

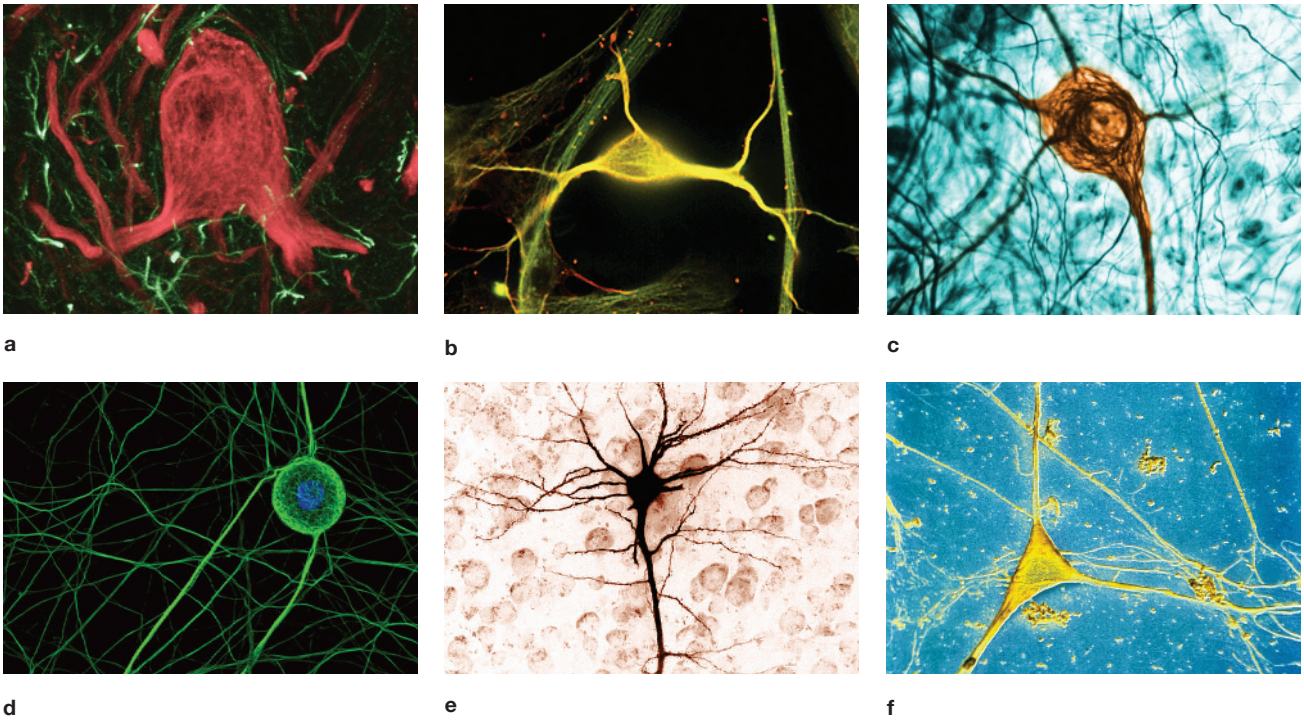
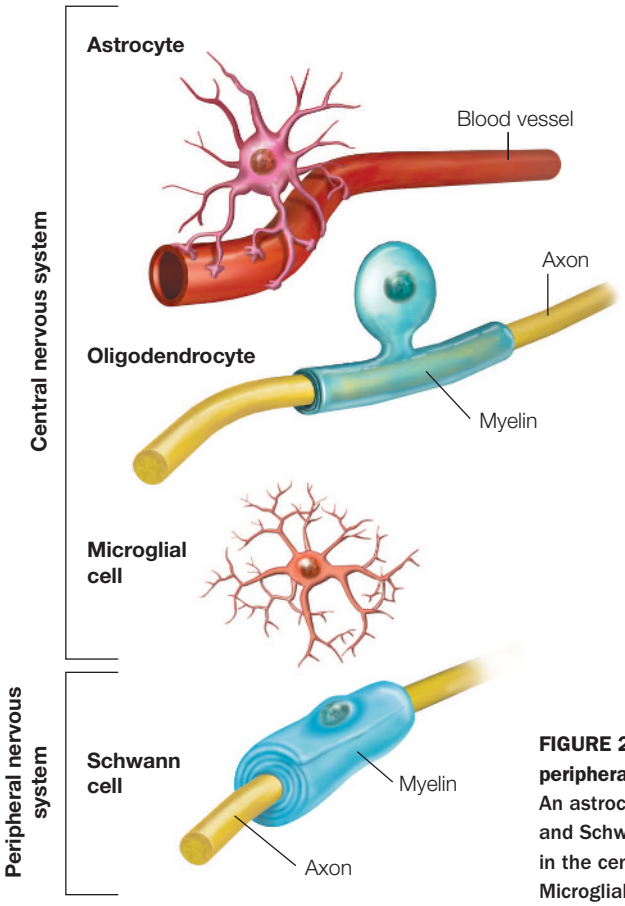


FIGURE 2.2 Mammalian neurons show enormous anatomical variety.
(a) Neuron (red) from the vestibular area of the brain. Glial cells are the thin, lighter structures (confocal light micrograph). **(b)** Hippocampal neuron (yellow; fluorescent micrograph). **(c)** Neuron (brown) in mouse dorsal root ganglion of the spinal cord (transmission electron micrograph). **(d)** Neuron in cell culture from dorsal root ganglia of an embryonic rat (fluorescent micrograph). **(e)** Pyramidal neuron from the brain. **(f)** Multipolar neuron cell body from human cerebral cortex (scanning electron micrograph).



astrocytes either directly or indirectly regulate the reuptake of neurotransmitters.

Glial cells also form the fatty substance called **myelin** in the nervous system. In the central nervous system, *oligodendrocytes* form myelin; in the peripheral nervous system, *Schwann cells* carry out this task (Figure 2.3). Both glial cell types create myelin by wrapping their cell membranes around the axon in a concentric manner during development and maturation. The cytoplasm in that portion of the glial cell is squeezed out, leaving layers of the lipid bilayer of the glial cell sheathing the membrane. Myelin is a good electrical insulator, preventing loss of electrical current across the cell membrane. It increases the speed and distance that information can travel along a neuron.

Microglial cells, which are small and irregularly shaped (Figure 2.3), are phagocytes that devour and remove damaged cells. Unlike many cells in the central nervous system, microglial cells can proliferate even in adults (as do other glial cells).

FIGURE 2.3 Various types of glial cells in the mammalian central and peripheral nervous systems.
An astrocyte is shown with end feet attached to a blood vessel. Oligodendrocytes and Schwann cells produce myelin around the axons of neurons (oligodendrocytes in the central nervous system, Schwann cells in the peripheral nervous system). Microglial cells dispose of damaged cells.

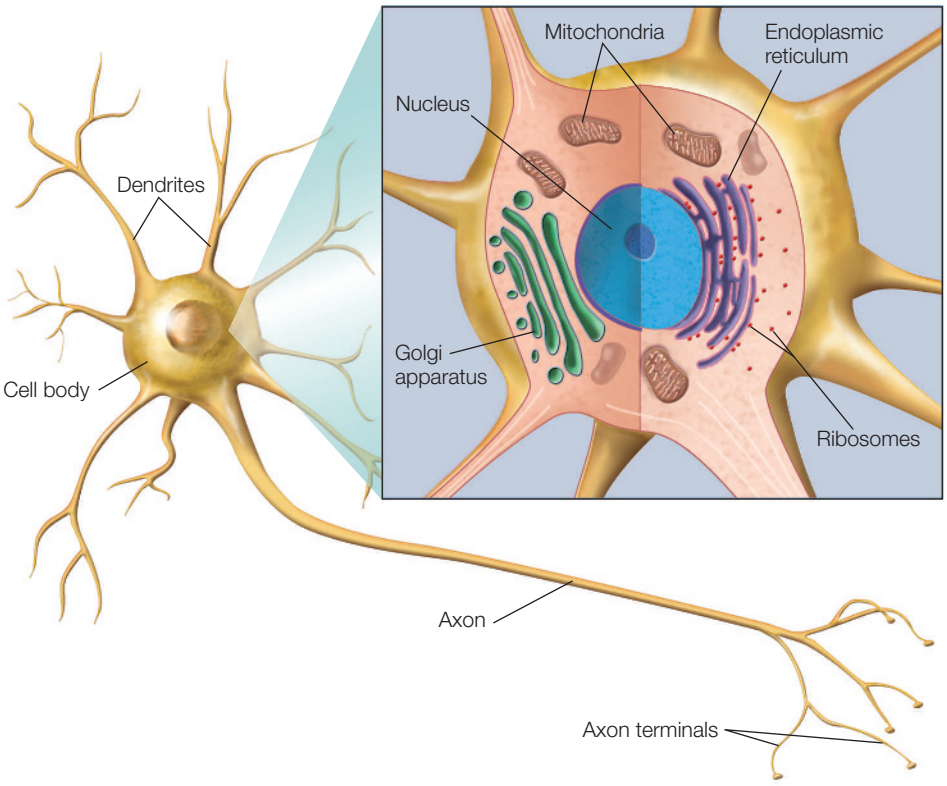


FIGURE 2.4 Idealized mammalian neuron.
A neuron is composed of three main parts: a cell body, dendrites, and an axon. The cell body contains the cellular machinery for the production of proteins and other macromolecules. Like other cells, the neuron contains a nucleus, endoplasmic reticulum, ribosomes, mitochondria, Golgi apparatus, and other intracellular organelles (inset). The dendrites and axon are extensions of the cell membrane and contain cytoplasm continuous with the cytoplasm inside the cell body.

Neurons

The standard cellular components found in almost all eukaryotic cells are also found in neurons (as well as in glial cells). A cell membrane encases the cell body (in neurons, it is sometimes called the **soma**; Greek for "body"), which contains the metabolic machinery that maintains the neuron: nucleus, endoplasmic reticulum, cytoskeleton, mitochondria, Golgi apparatus, and other common intracellular organelles (**Figure 2.4**). These structures are suspended in cytoplasm, the salty intracellular fluid that is made up of a combination of ions (molecules or atoms that have either a positive or negative electrical charge)—predominantly ions of potassium, sodium, chloride, and calcium—as well as molecules such as proteins. The neuron itself, like any other cell, sits in a bath of salty extracellular fluid, which is made up of a mixture of the same types of ions.

In addition, however, neurons possess unique cytological features and physiological properties that enable them to transmit and process information rapidly. The two predominant cellular components unique to neurons are the dendrites and the axon. **Dendrites** are branching extensions of the neuron that receive inputs from other neurons. They have many varied and complex forms, depending on the type and location of the neuron. The arborizations may look like the branches and twigs of an oak tree, as seen in the complex dendritic structures of the cerebellar Purkinje cells (**Figure 2.5**), or they may be

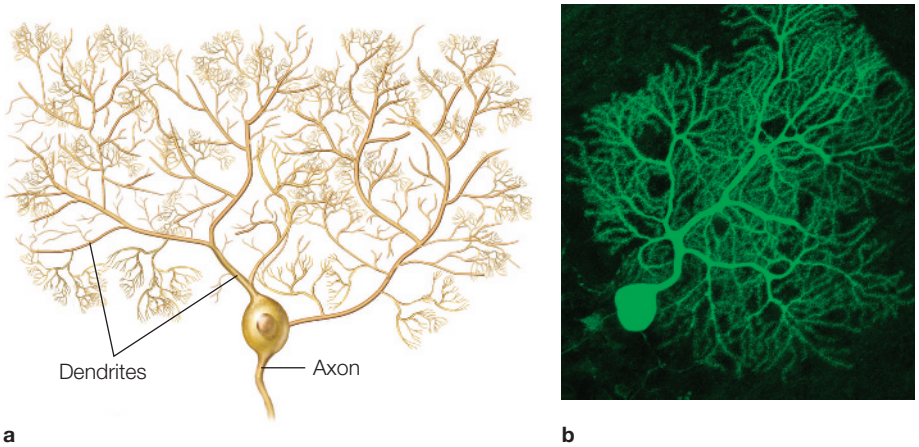


FIGURE 2.5 Soma and dendritic tree of a Purkinje cell from the cerebellum.
The Purkinje cells are arrayed in rows in the cerebellum. Each one has a large dendritic tree that is wider in one direction than the other. **(a)** Drawing of Purkinje cell as viewed in a cross section through a cerebellar folium. **(b)** Confocal micrograph of a Purkinje cell from mouse cerebellum. The cell is visualized using fluorescence methods.

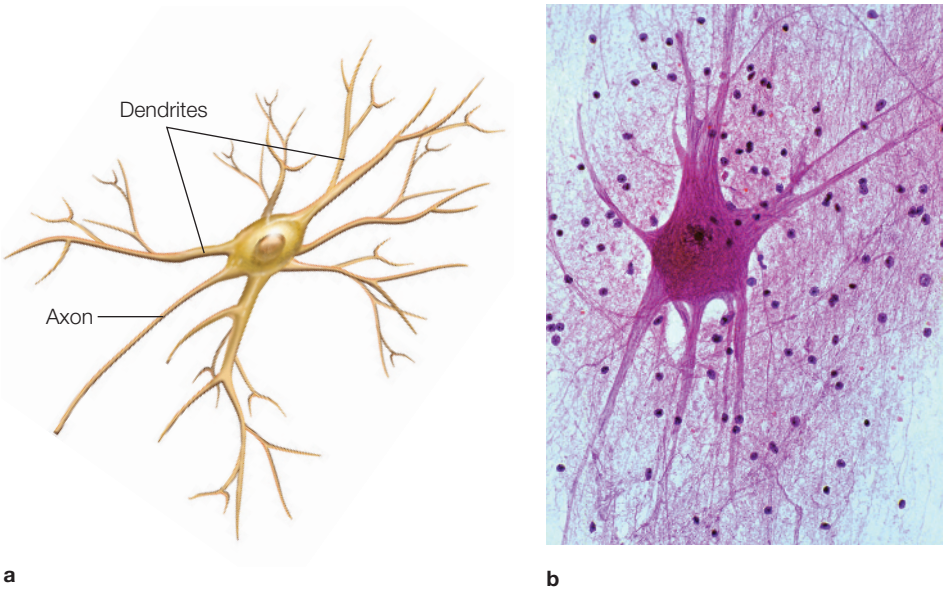


FIGURE 2.6 Spinal motor neuron.
(a) Neurons located in the ventral horn of the spinal cord send their axons out the ventral root to make synapses on muscle fibers. **(b)** A spinal cord motor neuron stained with cresyl echt violet stain.

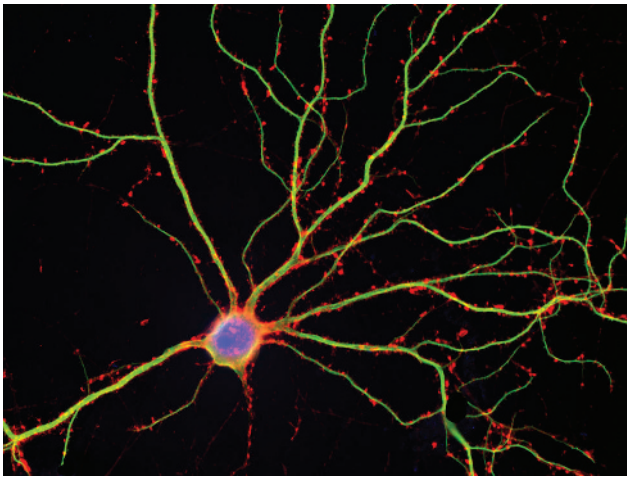


FIGURE 2.7 Dendritic spines on cultured rat hippocampal neurons.
This neuron has been triple stained to reveal the cell body (blue), dendrites (green), and spines (red).

much simpler, such as the dendrites in spinal motor neurons (**Figure 2.6**). Most dendrites also have specialized processes called **spines**, little knobs attached by small necks to the surface of the dendrites, where the dendrites receive inputs from other neurons (**Figure 2.7**).

The **axon** is a single process that extends from the cell body. This structure represents the output side of the neuron. Electrical signals travel along the length of the axon to its end, the axon terminals, where the neuron transmits the signal to other neurons or other targets. Transmission occurs at the **synapse**, a specialized structure where two neurons come into close contact so that chemical or electrical signals can be passed from one cell to the next. Some axons branch to form **axon collaterals** that can transmit signals to more than one cell (**Figure 2.8**).

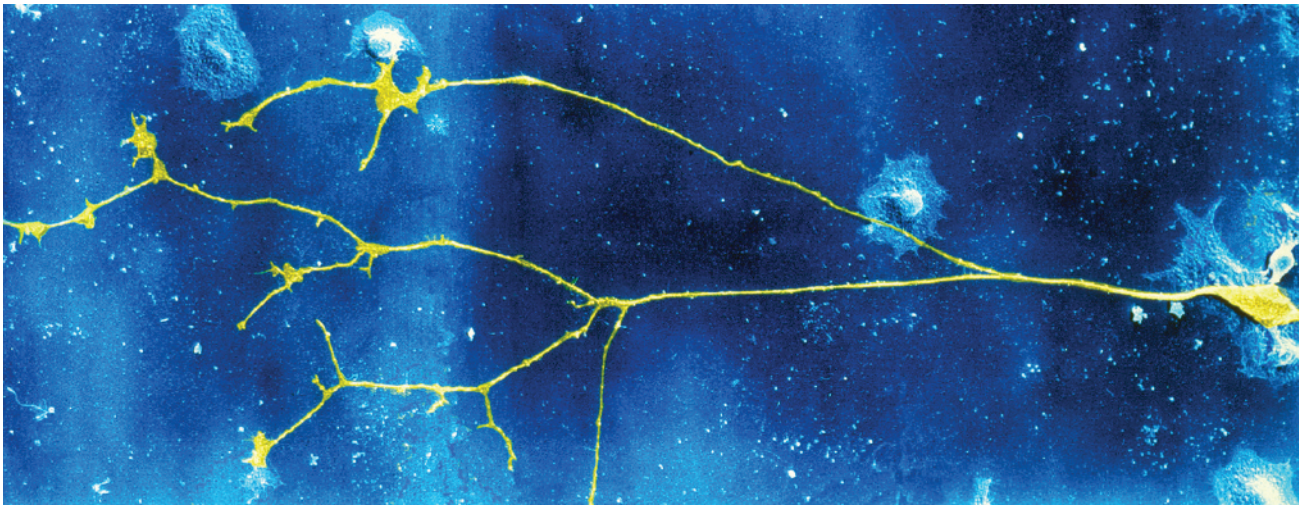


FIGURE 2.8 Axons can take different forms.
A neuron (far right) and its axon collaterals (left half of image) are shown stained in yellow. The cell body (at far right) gives rise to an axon, which branches, forming collaterals that can make contact with many different neurons.

Many axons are wrapped in layers of myelin. Along the length of the axons, there are evenly spaced gaps in the myelin; these gaps are commonly referred to as nodes of Ranvier (see Figure 2.12). Later, when we look at how signals move down an axon, we will explore the role of myelin and the nodes of Ranvier in accelerating signal transmission.

Neuronal Signaling

Neurons receive, evaluate, and transmit information. These processes are referred to as *neuronal signaling*. Information that is received by the neuron at its input synapses passes through the cell body and then, via the axon, to output synapses on the axon terminals. At these output synapses, information is transferred across synapses from one neuron to the next neuron; or to nonneuronal cells such as those in muscles or glands; or to other targets, such as blood vessels.

Within a neuron, information moves from input synapses to output synapses through changes in the electrical state of the neuron caused by the flow of electrical currents within the neuron and across its neuronal membrane. *Between* neurons, information transfer across synapses is typically mediated chemically by neurotransmitters (signaling molecules); these synapses are called *chemical synapses*. At *electrical synapses*, however, signals between neurons travel via transsynaptic electrical currents. Regarding information flow, neurons are referred to as either presynaptic or postsynaptic in relation to any particular synapse. *Most neurons are both presynaptic and postsynaptic:* They are **presynaptic** when their axon's output synapses make connections onto other neurons or targets, and they are **postsynaptic** when other neurons make a connection at input synapses onto their dendrites or elsewhere on the receiving neuron.

THE MEMBRANE POTENTIAL

The process of signaling has several stages. Let's return to Delgado's bull, whose neurons process information in the same way ours do. The bull is snorting about in the dirt, head down, when suddenly a sound wave—produced by Delgado entering the ring—courses down its auditory canal and hits the tympanic membrane (eardrum). The resultant stimulation of the auditory receptor cells (auditory hair cells) generates neuronal signals that are transmitted via the auditory pathways to the brain. At each stage of this ascending auditory pathway, neurons receive inputs on their dendrites that typically cause them to generate signals that are transmitted to the next neuron in the pathway.

How does the neuron generate these signals, and what are these signals? To answer these questions, we have to understand several things about neurons. First, energy is needed to generate the signals. Second, this energy is in the form of an electrical potential across the neuronal membrane. This electrical potential is defined as the difference in voltage across the neuronal membrane or, put simply, the voltage inside the neuron versus outside the neuron. Third, these two voltages depend on the concentrations of potassium, sodium, and chloride ions, as well as on charged protein molecules both inside and outside of the cell. Fourth, when a neuron is in its resting state and not actively signaling, the inside of a neuron is more negatively charged than the outside. The voltage difference across the neuronal membrane in the resting state is typically about −70 millivolts (mV) inside, which is known as the *resting potential* or **resting membrane potential**. This electrical-potential difference means that the neuron has at its disposal a kind of battery; and like a battery, the stored energy can be used to do work—signaling work (**Figure 2.9**).

How does the neuron generate and maintain this resting potential, and how does it use it for signaling? To answer these questions about function, we first need to examine the structures in the neuron that are involved in signaling. The bulk of the *neuronal membrane* is a bilayer of fatty lipid molecules that separates the cytoplasm from the extracellular milieu. Because the membrane is composed of lipids, it does not dissolve in the watery environments found inside and outside of the neuron, and it blocks the flow of water-soluble substances between the inside and the outside. It prevents ions, proteins, and other water-soluble molecules from moving across it. To understand neuronal signaling, we must focus on ions. This point is important: The lipid membrane maintains the separation of intracellular and extracellular ions and electrical charge that ultimately permits neuronal communication.

The neuronal membrane, though, is not merely a lipid bilayer. The membrane is peppered with transmembrane proteins, some of which serve as conduits for ions to move across the membrane (Figure 2.9, inset). These proteins are of two main types: ion channels and ion pumps. **Ion channels**, as we will see, are proteins with a pore through the center, and they allow certain ions to flow down their electrochemical and concentration gradients. **Ion pumps** use energy to actively transport ions across the membrane against their concentration gradients—that is, from regions of low concentration to regions of higher concentration.

Ion channels. The transmembrane passageways created by ion channels are formed from the three-dimensional structure of these proteins. These hydrophilic channels selectively permit one type of ion to pass through the membrane. The ion channels of concern to us—the ones found in neurons—are selective for sodium, potassium,

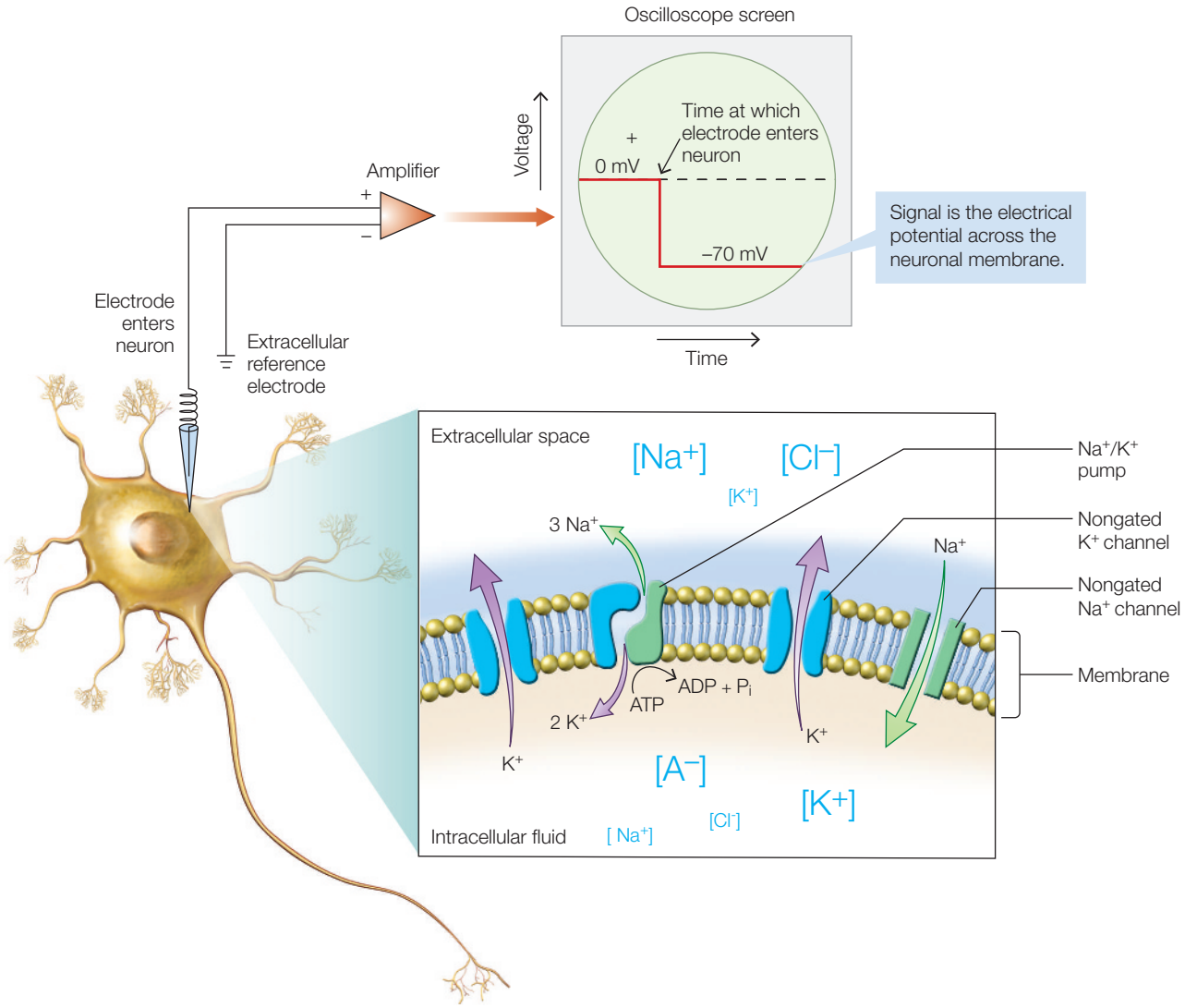


FIGURE 2.9 Ion channels in a segment of neuronal membrane and measuring resting membrane potential.
Idealized neuron (left), shown with an intracellular recording electrode penetrating the neuron. The electrode measures the difference between the voltage inside versus outside the neuron, and this difference is amplified and displayed on an oscilloscope screen (top). The oscilloscope screen shows voltage over time. Before the electrode enters the neuron, the voltage difference between the electrode and the extracellular reference electrode is zero, but when the electrode is pushed into the neuron, the difference becomes −70 mV, which is the resting membrane potential. The resting membrane potential arises from the asymmetrical distribution of ions of sodium (Na^+), potassium (K^+), and chloride (Cl^-), as well as of charged protein molecules (A^-), across the neuron's cell membrane (inset).

calcium, or chloride ions (Na^+, K^+, Ca^{2+}, and Cl^-, respectively; Figure 2.9, inset). The extent to which a particular ion can cross the membrane through a given ion channel is referred to as its **permeability**. This characteristic of ion channels gives the neuronal membrane the attribute of *selective permeability*. (Selective permeability is actually a property of all cells in the body; as part of cellular homeostasis, it enables cells to maintain internal chemical stability.) The neuronal membrane is more permeable to K^+ than to Na^+ (or other) ions—a property that contributes to the resting membrane potential, as we will learn shortly. The membrane permeability to K^+ is larger because there are many more K^+-selective channels than any other type of ion channel.

Unlike most cells in the body, neurons are excitable, meaning that their membrane permeability can change (because the membranes have ion channels that are capable of changing their permeability for a particular ion). Such proteins are called *gated ion channels*. They open or close in response to changes in nearby transmembrane voltage, or to chemical or physical stimuli. In contrast, ion channels that are unregulated, and hence always allow the associated ion to pass through, are known as *nongated ion channels*.

Ion pumps. Under normal conditions, Na^+ and Cl^- concentrations are greater outside the cell, and K^+ concentrations are greater inside the cell. You may be wondering why K^+ ions don't flow out of the neuron—down their concentration gradient—until the K^+ ion concentrations inside and outside the cell are equal. We could ask the corresponding question for all other ions.

To combat this drive toward equilibrium, neurons use *active transport* proteins known as ion pumps. In particular, neurons use a Na^+/K^+ pump that pumps Na^+ ions out of the cell and K^+ ions into the cell (Figure 2.9, inset). Because this process moves ions up their concentration gradients, the mechanism requires energy. Each pump is an enzyme that hydrolyzes adenosine triphosphate (ATP) for energy. For each molecule of ATP that is hydrolyzed, enough energy is produced to move three Na^+ ions out of the cell and two K^+ ions into the cell (**Figure 2.10**).

The concentration gradients create forces due to the unequal distribution of ions. The force of the Na^+ concentration gradient acts to push Na^+ from an area of high concentration to one of low concentration (from outside to inside), while the K^+ concentration gradient acts to push K^+ also from an area of high concentration to an area of low concentration (from inside to outside)—the very thing the pump is working against. With both positively and negatively charged ions inside and outside the cell, why is the voltage different inside versus outside the neuron?

The inside and outside voltages are different because the membrane is more permeable to K^+ than to Na^+. The force of the K^+ concentration gradient pushes some K^+ out of the cell, leaving the inside of the neuron slightly more negative than the outside. This difference creates another force, an **electrical gradient**, because each K^+ ion carries one unit of positive charge out of the neuron as it moves across the membrane. These

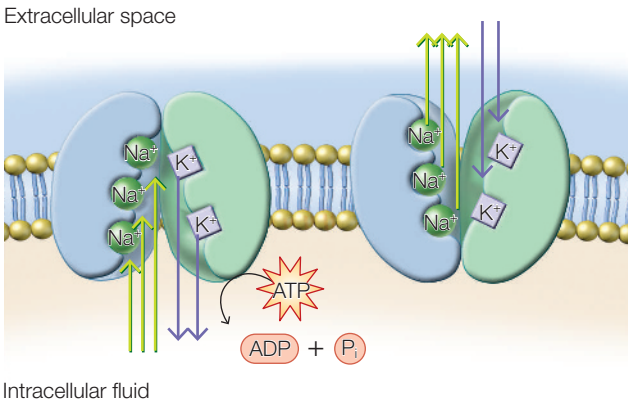


FIGURE 2.10 Ion pumps transport ions across the membrane. The Na^+/K^+ pump preserves the cell's resting potential by maintaining a larger concentration of K^+ inside the cell and Na^+ outside the cell. The pump uses ATP as energy.

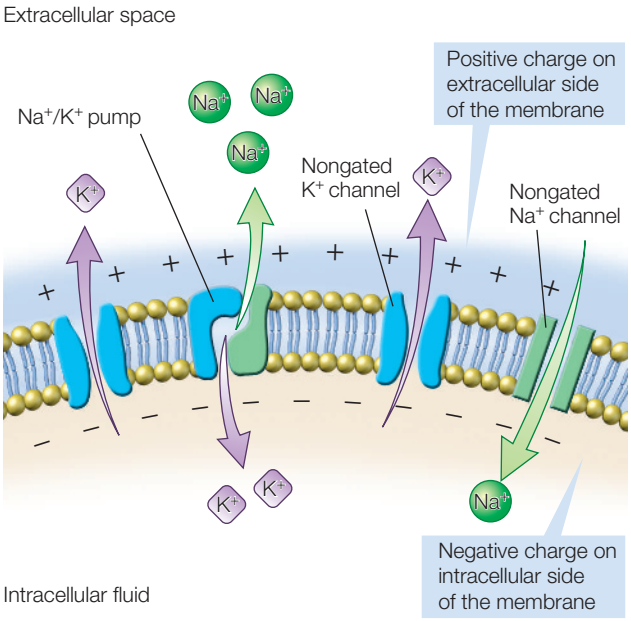


FIGURE 2.11 Selective permeability of the membrane. The membrane's selective permeability to some ions, and the concentration gradients formed by active pumping, lead to a difference in electrical potential across the membrane; this is the *resting membrane potential*. The membrane potential, represented here by the positive charges outside the neuron along the membrane and the negative charges inside along the membrane, is the basis for the transmembrane voltage difference shown in Figure 2.9.

two gradients (electrical and ionic concentration) are in opposition to one another with respect to K^+ (**Figure 2.11**).

As negative charge builds up along the inside of the membrane (and an equivalent positive charge forms along the extracellular side), the positively charged K^+ ions outside of the cell are drawn electrically back into the neuron through the same ion channels that are allowing K^+ ions to leave the cell by diffusion. Eventually, the force of the concentration gradient pushing K^+ out through the K^+ channels is equal to the force of the electrical gradient driving K^+ in. When that happens, the opposing forces are said to reach *electrochemical equilibrium*. The difference in charge thus produced across the membrane is the resting membrane potential, that –70 mV difference. The value for the resting membrane potential of any cell can be calculated by using knowledge from electrochemistry, provided that the concentrations of ions inside and outside the neuron are known.

THE ACTION POTENTIAL We now understand the basis of the energy source that neurons can use for signaling. Next we want to learn how this energy can be used to transmit information within a neuron, from its dendrites, which receive inputs from other neurons, to its axon terminals, where it signals to the next neuron(s)

in the chain. The process begins when synapses on a neuron's dendrites receive a signal (e.g., a neurotransmitter binding to a receptor), resulting in the opening of ion channels in the dendrite, which causes ionic currents to flow. For excitatory synaptic inputs, *excitatory postsynaptic potentials (EPSPs)* occur in the dendrite, and ionic currents flow through the volume of the neuron's cell body. If these currents happen to be strong enough to reach distant axon terminals, then the process of neuronal signaling is complete. In the vast majority of cases, however, the distance from dendrites to axon terminals is too great for the EPSP to have any effect. Why?

The small electrical current produced by the EPSP is passively conducted through the cytoplasm of the dendrite, cell body, and axon. Passive current conduction is called **electrotonic conduction** or *decremental conduction:* "decremental" because it diminishes with distance from its origin—the synapse on the dendrites, in this case. The maximum distance a passive current will flow in a neuron is only about 1 mm. In most neurons, a millimeter is too short to effectively conduct electrical signals, although sometimes, like in a structure such as the retina, a millimeter is sufficient to permit neuron-to-neuron communication via decremental conduction. Most of the time, however, the reduction in signal intensity with decremental conduction means that long-distance communication within a neuron from dendrite to axon terminal will fail (your toes would be in trouble, for example, because they are about 1 meter from the spinal cord and close to 2 meters from the brain). How does the neuron solve this problem of decremental conduction and the need to conduct signals over long distances?

Neurons evolved a clever mechanism to regenerate and pass along the signal received at synapses on the dendrite: the **action potential**. It works something like 19th-century firefighters in a bucket brigade. An action potential is a rapid depolarization and repolarization of a small region of the membrane on the neuron's output via its axon caused by the opening and closing of ion channels.

An action potential is a different process from the EPSP and the ionic currents involved in decremental conduction. The action potential doesn't decrement after only 1 mm. Action potentials enable signals to travel for meters with no loss in signal strength, because they continually regenerate the signal at each patch of membrane on the axon. This is one reason why giraffes and blue whales can have neurons whose axon terminals may be many meters from their dendrites.

The action potential is able to regenerate itself because of the presence of **voltage-gated ion channels** located in the neuronal membrane (**Figure 2.12a**, inset). The densest concentration of ion channels is found at the

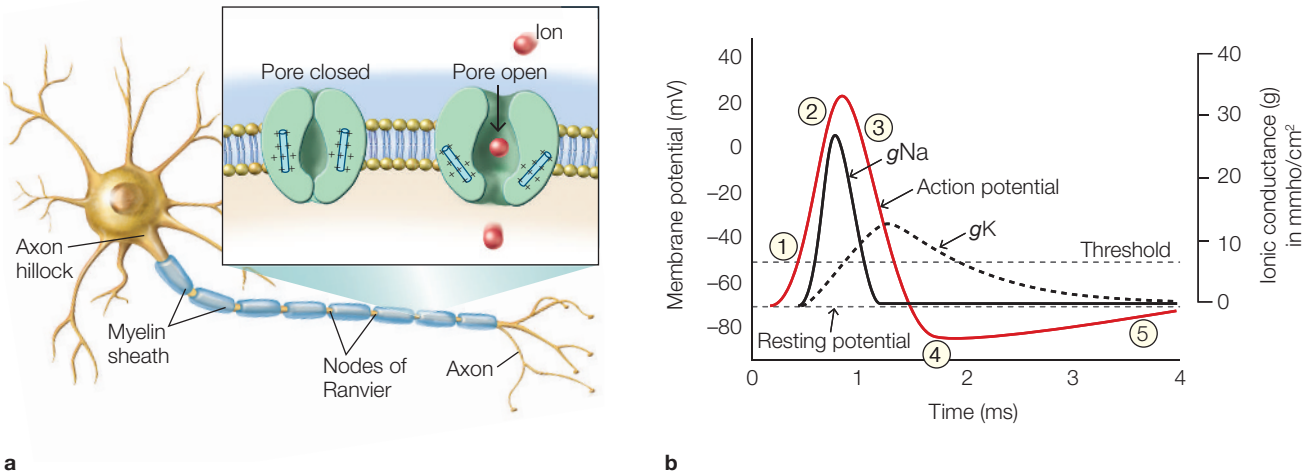


FIGURE 2.12 The neuronal action potential, voltage-gated ion channels, and changes in channel conductance.

(a) An idealized neuron with myelinated axon and axon terminals. Voltage-gated ion channels located in the spike-triggering zone at the axon hillock and along the extent of the axon at the nodes of Ranvier open and close rapidly, changing their conductance to specific ions (e.g., Na^+), altering the membrane potential and resulting in the action potential (inset). **(b)** The relative time course of changes in membrane voltage during an action potential, and the underlying causative changes in membrane conductance to Na^+ (gNa) and K^+ (gK). The initial depolarizing phase of the action potential (red line) is mediated by increased Na^+ conductance (black line), and the later repolarizing, descending phase of the action potential is mediated by an increase in K^+ conductance (dashed line) that occurs when the K^+ channels open. The Na^+ channels have closed during the last part of the action potential, when repolarization by the K^+ current is taking place. The action potential undershoots the resting membrane potential at the point where the membrane becomes more negative than the resting membrane potential.

spike-triggering zone in the **axon hillock**, a specialized region of the neuronal soma where the axon emerges. As its name denotes, the spike-triggering zone initiates the action potential. (The term *spike* is shorthand for an action potential because it represents a rapid change and a peak in the depolarization of the membrane potential, and it actually looks like a spike when viewed as a recording displayed on an oscilloscope or computer screen.) Ion channels are also found along the axon. In myelinated axons, voltage-gated ion channels along the axon's length are restricted to the **nodes of Ranvier**. Named after the French histologist and anatomist Louis-Antoine Ranvier, who first described them, they are regular intervals along the axon where gaps in myelination occur (Figure 2.12a).

How does the spike-triggering zone initiate an action potential? The passive electrical currents that are generated following EPSPs on multiple distant dendrites sum together at the axon hillock. This current flows across the neuronal membrane in the spike-triggering zone, depolarizing the membrane. If the depolarization is strong enough, meaning that the membrane moves from its resting potential of about –70 mV to a less negative value of approximately –55 mV, then an action potential is triggered. We refer to this **depolarized** membrane potential value as the **threshold** for initiating an action potential. **Figure 2.12b** illustrates an idealized action potential. The numbered circles in the figure correspond to the numbered events in the next paragraph. Each event alters a small region of the membrane's permeability for Na^+ and K^+ as a result of the opening and closing of voltage-gated ion channels.

When the threshold (Figure 2.12b, event 1) is reached, voltage-gated Na^+ channels open and Na^+ flows rapidly into the neuron. This influx of positive ions further depolarizes the neuron, opening additional voltage-gated Na^+ channels; thus, the neuron becomes more depolarized (2), continuing the cycle by causing even more Na^+ channels to open. This process is called the Hodgkin–Huxley cycle. This rapid, self-reinforcing cycle, lasting only about 1 ms, generates the large depolarization that is the first portion of the action potential. Next, the voltage-gated K^+ channels open, allowing K^+ to flow out of the neuron down its concentration gradient. This outward flow of positive ions begins to shift the membrane potential back toward its resting potential (3). The opening of the K^+ channels outlasts the closing of the Na^+ channels, causing a second repolarizing phase of the action potential; this repolarization drives the membrane potential toward the equilibrium potential of K^+, which is even more negative than the resting potential. The **equilibrium potential** is the membrane potential at which there is no net flux of a given ion. As a result, the membrane is temporarily **hyperpolarized**: At about –80 mV, the membrane potential is more negative than both the resting membrane potential and the threshold required for triggering an action potential (4). Hyperpolarization causes the K^+ channels to close, in response to which the membrane potential gradually returns to its resting state (5).

During this transient hyperpolarization state, the voltage-gated Na^+ channels are unable to open, and no other action potential can be generated. This is known as the *absolute refractory period*. It is followed by the *relative refractory period*, during which the neuron can generate action potentials, but only with larger-than-normal depolarizing currents. The entire **refractory period** lasts only a couple of milliseconds and has two consequences. One is that the neuron's speed for generating action potentials is limited to about 200 action potentials per second. The other is that the passive current that flows from the action potential cannot reopen the ion-gated channels that generated it. The passive current, however, does flow down the axon with enough strength to depolarize the membrane a bit farther on, where the ion channels are not in a refractory state, opening voltage-gated channels in this next portion of the membrane. The result is that the action potential moves down the axon in one direction only—from the axon hillock toward the axon terminal.

That is the story of the self-regenerating action potential as it propagates itself down an axon, sometimes traveling several meters in the process. But traveling far is not the end of the story. Action potentials must also travel quickly if a person wants to run, or a bull wants to charge, or a very large animal (think blue whale) simply wants to react in a reasonable amount of time. Accelerated transmission of the action potential is accomplished in myelinated axons. The thick lipid sheath of myelin (Figure 2.12a) surrounding the membrane of myelinated axons makes the axon super-resistant to voltage loss. The high electrical resistance allows passive currents generated by the action potential to be shunted farther down the axon. The result is that action potentials do not have to be generated as often, and they can be spread out along the axon at wider intervals.

Indeed, action potentials in myelinated axons need occur only at the nodes of Ranvier, where myelination is interrupted. As a result, the action potential appears to jump down the axon at great speed, from one node of Ranvier to the next. We call this **saltatory conduction** (the term is derived from the Latin word *saltare*, meaning "to jump or leap"). The importance of myelin for efficient neuronal conduction is notable when it is damaged or lost, which is what happens in multiple sclerosis (MS).

There is one more interesting tidbit concerning action potentials: Because they always have the same amplitude, they are said to be *all-or-none* phenomena. Since one action potential has the same amplitude as any other, the strength of the action potential does not communicate anything about the strength of the stimulus that initiated it. The intensity of a stimulus (e.g., a sensory signal) is communicated by the *rate of firing* of the action potentials: More intense stimuli elicit higher action-potential firing rates.

NEURAL OSCILLATIONS So far, we have presented an idealized situation: A neuron is sitting in a resting state, awaiting inputs that might cause it to experience EPSPs and action potentials at the axon hillock that move down the axon to transmit signals. But most neurons actually fire at a continuous baseline rate. This rate is different in different types of neurons, and it can be the result of either intrinsic properties of the neuron itself or activity in small neural circuits or larger neural networks. These neuronal oscillations are important for understanding some of the signals we can receive from electrodes placed in an intact brain or on the surface of the scalp. Because postsynaptic potentials like EPSPs can be recorded from populations of neurons, they are another measure of neuronal activity in addition to recordings of action potentials. In Chapter 3 we describe how these postsynaptic potentials, and not the action potentials, are the sources of electrical signals that can be recorded from the cortical surface or scalp in humans and animals using electroencephalography.

TAKE-HOME MESSAGES

- Glial cells form myelin around the axons of neurons. Myelin enables the rapid transmission of action potentials down an axon and increases the distance over which transmission can occur.
- Neurons communicate with other neurons and cells at specialized structures called synapses, where chemical and electrical signals can be conveyed between neurons.
- The electrical gradient across a neuron's membrane results from the asymmetrical distribution of ions. The electrical difference across the membrane is the basis of the resting potential, the voltage difference across the neuronal membrane during rest (i.e., not during any phase of the action potential).
- Ion channels, formed by transmembrane proteins, can be either passive (always open) or gated (open only in the presence of electrical, chemical, or physical stimuli).
- Synaptic inputs result in postsynaptic potentials, and current to flow in the postsynaptic neuron.
- Postsynaptic currents can depolarize the axon hillock region, generating an action potential.
- Action potentials are all-or-none phenomena: The amplitude of the action potential does not depend on the size of the triggering depolarization, as long as that depolarization reaches the threshold for initiating the action potential.
- Nodes of Ranvier are the spaces between sheaths of myelin where voltage-gated Na^+ and K^+ channels are located and action potentials occur.
- Postsynaptic potentials lead to action potentials but also can be measured from large populations of neurons by electrodes located some distance away, such as the scalp, as when the oscillatory signals in an electroencephalogram (EEG) are being recorded.

2.2 Synaptic Transmission

Neurons communicate with other neurons, with muscles, or with glands at synapses, and the transfer of a signal from the axon terminal of one neuron to the next neuron is called *synaptic transmission*. There are two major kinds of synapses—chemical and electrical—each using very different mechanisms for synaptic transmission.

Chemical Transmission

Most neurons send a signal to the cell across the synapse by releasing chemical neurotransmitters into the **synaptic cleft**, the gap between neurons at the synapse. The general mechanism is as follows: The arrival of the action potential at the axon terminal leads to depolarization of the terminal membrane, causing voltage-gated Ca^{2+} channels to open. The opening of these channels triggers small **vesicles** containing neurotransmitter to fuse with the membrane at the synapse and release the transmitter into the synaptic cleft. Different neurons produce and release different neurotransmitters, and some may release more than one type at a time, in what is called co-transmission. The transmitter diffuses across the cleft and, on reaching the postsynaptic membrane, binds with specific receptors embedded in it (**Figure 2.13**).

There are two types of postsynaptic receptors: ligand-gated ion channels where neurotransmitter binding directly gates (opens) the ion channel, and G protein–coupled receptors (GPCRs) where biochemical signals indirectly cause the gating of ion channels; G proteins are those that bind the guanine nucleotides GDP and GTP (guanosine di- and triphosphate) and act as molecular switches in cells. Specific neurotransmitters bind to each type of postsynaptic receptor. In ligand-gated ion channels, binding induces a conformational change in the receptor. The change in shape opens an ion channel, resulting in an influx of ions

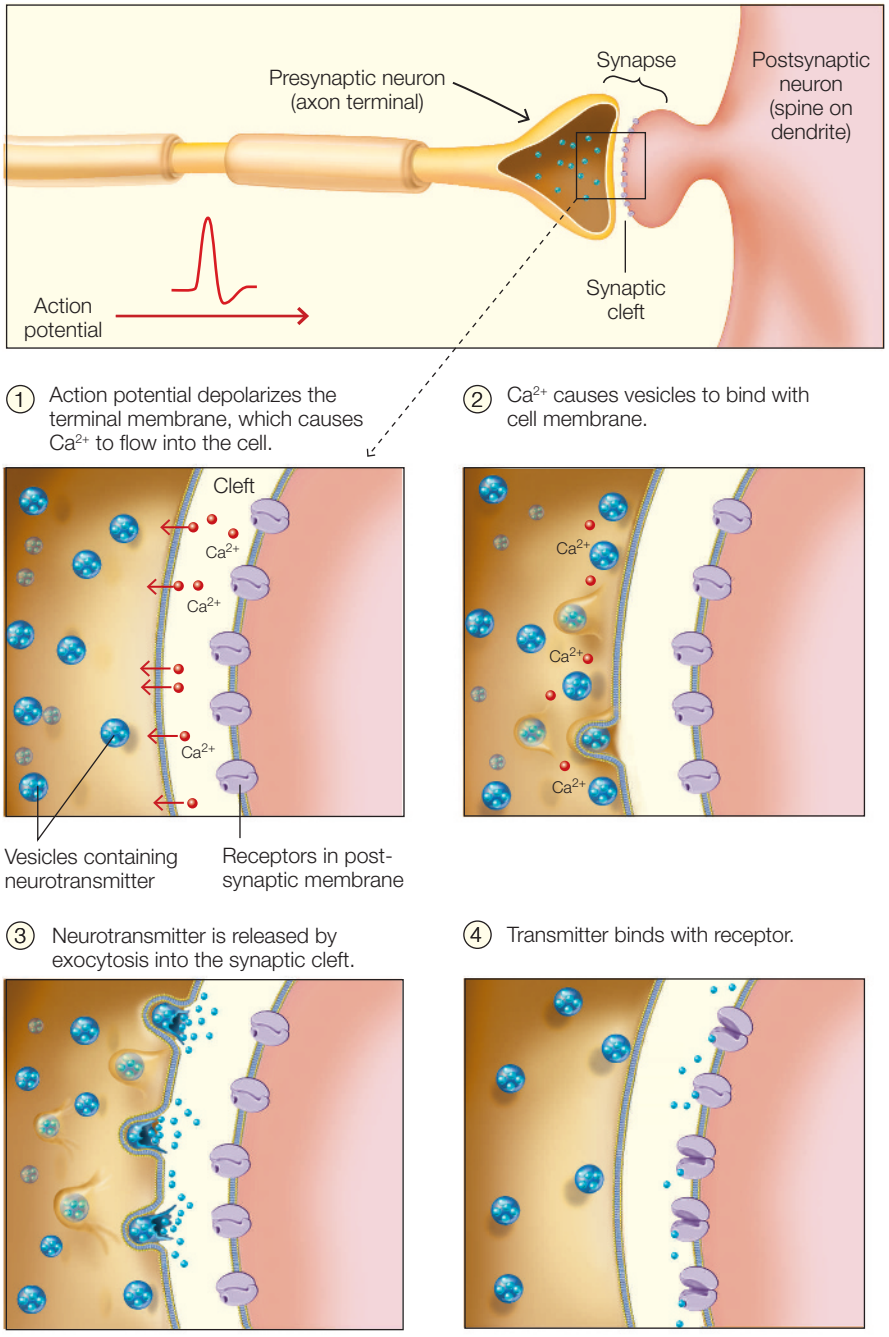


FIGURE 2.13 Neurotransmitter release at the synapse, into the synaptic cleft. The synapse consists of various specializations where the presynaptic and postsynaptic membranes are close together. When the action potential invades the axon terminals, it causes voltage-gated Ca^{2+} channels to open (1), triggering vesicles to bind to the presynaptic membrane (2). Neurotransmitter is released into the synaptic cleft by exocytosis and diffuses across the cleft (3). Binding of the neurotransmitter to receptor molecules in the postsynaptic membrane completes the process of transmission (4).

leading to either depolarization (excitation) or hyperpolarization (inhibition) of the postsynaptic cell (**Figure 2.14**). Hyperpolarization of the postsynaptic neuron produces an inhibitory postsynaptic potential (IPSP).

Excitatory and inhibitory neurons are also capable of modulating functions through the GPCRs. There are over 1,000 different GPCRs, giving us an idea of the complexity of the system. The particular GPCRs that are present depend on the neuron and where it is located. Each type of GPCR is activated by a specific signaling molecule, which could be a neurotransmitter, a neuropeptide (a small protein-like molecule secreted by neurons or glial cells), or a neurosteroid, among other possible signals.

When a signaling molecule specifically binds to its GPCR, the conformational change activates a G protein within the cell, which in turn activates or regulates a specific target protein, typically an enzyme, which produces a diffusible molecule of some sort called a *second messenger*. The second messenger, in turn, triggers a biochemical cascade of reactions. While directly gated channels mediate fast signaling, measured in milliseconds, GPCR-mediated signaling is slower, occurring over hundreds of milliseconds or even seconds and producing longer-lasting modulatory changes to the functional state. For example, the neurotransmitter epinephrine binds to a particular GPCR. Once bound, a G protein is activated that seeks

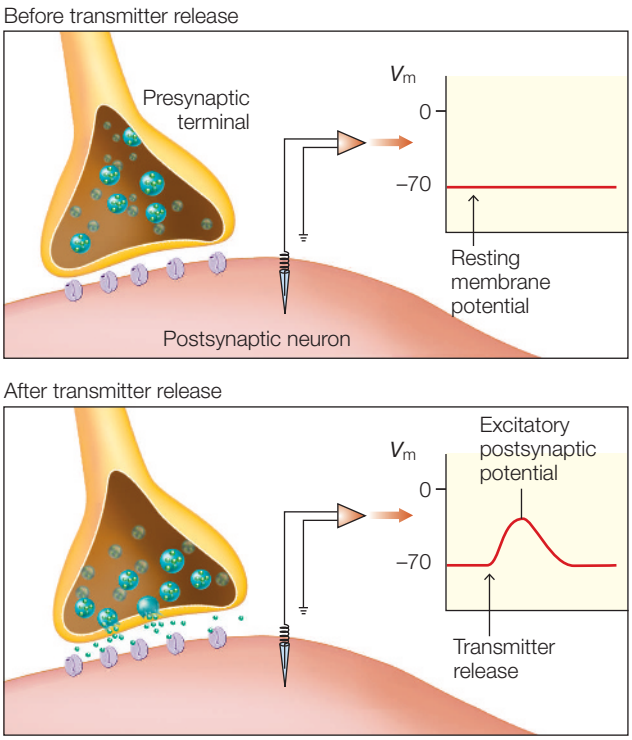


FIGURE 2.14 Neurotransmitter leading to a postsynaptic potential. The binding of neurotransmitter to the postsynaptic membrane receptors changes the membrane potential (V_m). These postsynaptic potentials can be either excitatory (depolarizing the membrane), as shown here, or inhibitory (hyperpolarizing the membrane).

out the protein adenylate cyclase and activates it. Activated adenylate cyclase turns ATP into cAMP (cyclic adenosine monophosphate), which acts as a second messenger of information instructing the postsynaptic neuron.

NEUROTRANSMITTERS While you may have heard of a few of the classic **neurotransmitters**, more than 100 have been identified. What makes a molecule a neurotransmitter?

- It is synthesized by and localized within the presynaptic neuron, and stored in the presynaptic terminal before release.
- It is released by the presynaptic neuron when action potentials depolarize the terminal (mediated primarily by Ca^{2+}).
- The postsynaptic neuron contains receptors specific for it.
- When artificially applied to a postsynaptic cell, it elicits the same response that stimulating the presynaptic neuron would.

Biochemical classification of neurotransmitters. Some neurotransmitters are amino acids: aspartate, gamma-aminobutyric acid (GABA), glutamate, and glycine. Another category of neurotransmitters, called *biogenic amines*, includes dopamine, norepinephrine, and epinephrine (these three are known as the catecholamines), serotonin (5-hydroxytryptamine), and histamine. Acetylcholine (ACh) is a well-studied neurotransmitter that is in its own biochemical class. Another large group of neurotransmitters consists of slightly larger molecules, the *neuropeptides*, which are made up of strings of amino acids. More than 100 neuropeptides are active in the mammalian brain, and they are divided into five groups:

1. *Tachykinins* (brain-gut peptides, which are peptides secreted by endocrine cells and enteric neurons in the GI tract and also neurons in the central nervous system). This group includes substance P, which affects vasoconstriction and is a spinal neurotransmitter involved in pain.
2. *Neurohypophyseal hormones.* Oxytocin and vasopressin are in this group. The former is involved in mammary functions and has been tagged the "love hormone" for its role in pair bonding and maternal behaviors; the latter is an antidiuretic hormone.
3. *Hypothalamic releasing hormones.* This group includes corticotropin-releasing hormone, involved in the stress response; somatostatin, an inhibitor of growth hormone; and gonadotropin-releasing hormone, involved with the development, growth, and functioning of the body's reproductive processes.
4. *Opioid peptides.* This group is named for its similarity to opiate drugs, and these peptides bind to opiate receptors. It includes the endorphins and enkephalins.
5. *Other neuropeptides.* This group includes peptides that do not fit neatly into another category, such as insulins, secretins (e.g., glucagon), and gastrins.

Some neurons produce only one type of neurotransmitter, but others produce multiple kinds. Neurons that do produce particular neurotransmitters sometimes form distinct systems, such as the cholinergic system, the noradrenergic system, the dopaminergic system, and the serotonergic system. When a neurotransmitter system is activated, large areas of the brain can be affected (**Figure 2.15**). Neurons that produce more than one type of transmitter may release them together or separately, depending on the conditions of stimulation. For example, the rate of stimulation by the action potential can induce the release of a specific neurotransmitter.

Functional classification of neurotransmitters. As mentioned earlier, the effect of a neurotransmitter on the postsynaptic neuron is determined by the postsynaptic receptor's properties rather than by the transmitter itself. A particular neurotransmitter may have more than one type of postsynaptic receptor to which it binds, mediating different responses. Thus, the same neurotransmitter released from the same presynaptic neuron onto two different postsynaptic cells might cause one to increase

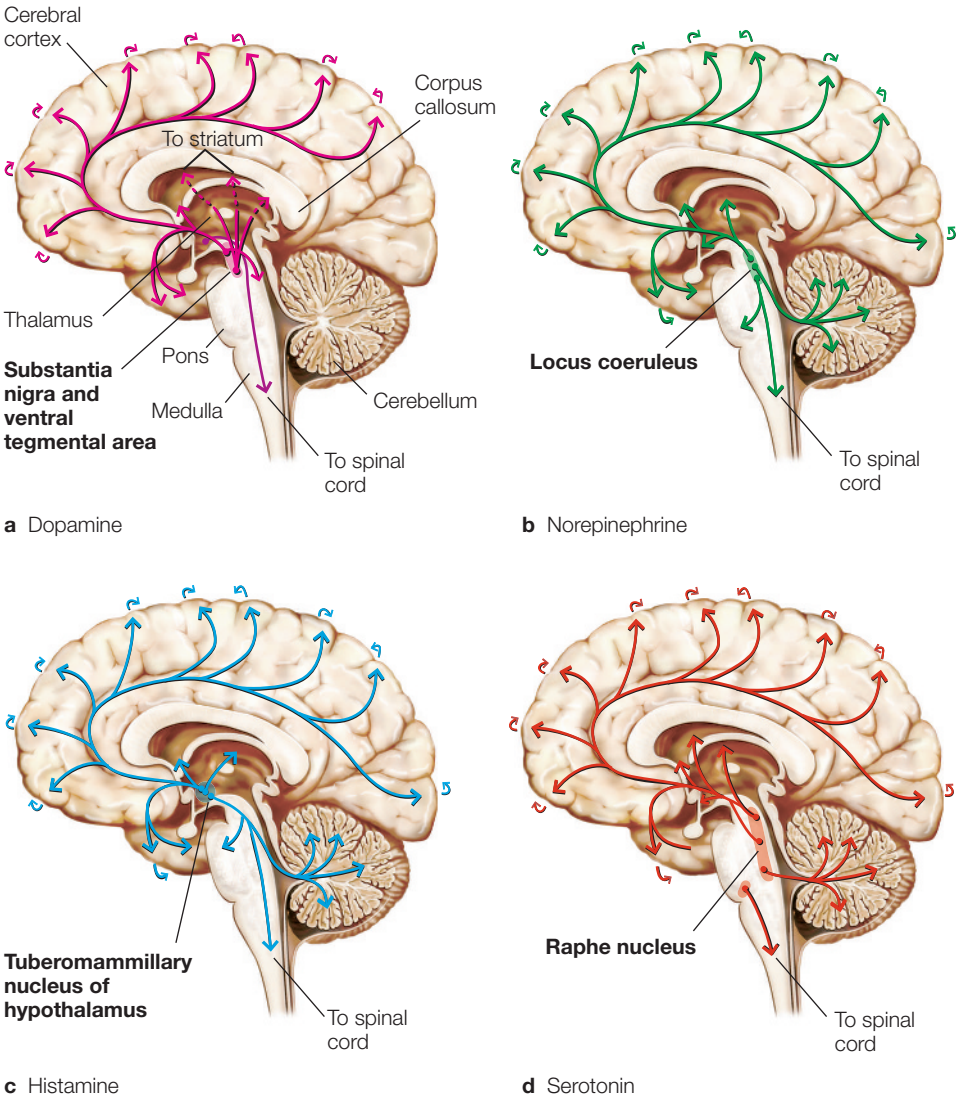


FIGURE 2.15 Major projection pathways of the biogenic amine neurotransmitter systems in the human brain.
Shown are the projections of the dopamine **(a)**, norepinephrine **(b)**, histamine **(c)**, and serotonin **(d)** systems using the neurotransmitters. The views are midsagittal cuts through the human brain, showing the medial surface of the right hemisphere; the frontal pole is at left. In each image, the primary source of the biogenic amine is in bold type.

firing and the other to decrease firing, depending on the receptors to which the transmitter binds.

The effects also depend on the concentration of the transmitter; the type, number, and density of the receptors; whether, when, and which co-neurotransmitters are also released; and the long-range connections of the neuron. For example, if different co-transmitters are released—one binding to a directly gated receptor with fast signaling and the other to a GPCR with slower signaling—they may produce opposite actions, and their overall combined effect may produce many possible outcomes, even complementary effects. Nevertheless, neurotransmitters can be classified not only biochemically, but also by the *typical effect* that they induce in the postsynaptic neuron.

Neurotransmitters that usually have an excitatory effect include ACh, the catecholamines, glutamate, histamine, serotonin, and some of the neuropeptides. Neurotransmitters that are typically inhibitory include GABA, glycine, and some of the neuropeptides. Some neurotransmitters act directly to excite or inhibit a postsynaptic neuron, but other neurotransmitters act only in concert with other factors. These are sometimes referred to as *conditional neurotransmitters* because their action is conditioned on the presence of another transmitter in the synaptic cleft or activity in the neural circuit. These types of mechanisms permit the nervous system to achieve complex modulations of information processing by modulating neurotransmission.

Some common neurotransmitters and their functions. The primary players in the balancing act between excitation and inhibition are glutamate and GABA. *Glutamate* is released by the pyramidal cells of the cortex, the most common cortical neurons. As a result, glutamate is the most prevalent neurotransmitter and is found in most of the fast excitatory synapses in the brain and spinal cord. A few different types of receptors bind glutamate, and some of these are found in modifiable synapses (i.e., ones that can change in strength) involved in learning and memory. Too much

glutamate (excitation) can be toxic and cause cell death and has been implicated in stroke, epilepsy, and neurodegenerative diseases such as Alzheimer's and Parkinson's.

GABA is the second most prevalent neurotransmitter and is synthesized from glutamate. It is found in most of the fast inhibitory synapses across the brain. As with glutamate, there is more than one type of GABA receptor, but the most common one opens Cl^- channels to allow an influx of negatively charged ions into the cell, negatively shifting (hyperpolarizing) the membrane potential and, in essence, inhibiting the neuron by making it much less likely to fire. GABA's role in information processing is varied and complex and is actively being researched.

Over the past few years, several populations of neurons that researchers believed released only glutamate, acetylcholine, dopamine, or histamine have also been found to release GABA (reviewed in Tritsch et al., 2016). For example, although glutamate and GABA have opposing functions, their co-release has recently been documented from individual CNS axons (in the ventral tegmental area and entopeduncular nucleus). Defects in the GABA system may be local or affect the entire CNS. Decreased levels of GABA (decreased inhibition) can result in seizures, as well as increases in emotional reactivity, heart rate, blood pressure, food and water intake, sweating, insulin secretion, gastric acid, and colonic motility. Too much GABA can lead to coma.

Acetylcholine (ACh) is present in the synapses between neurons and between neurons and muscles (neuromuscular junctions), where it has an excitatory effect and activates muscles. In the brain, ACh acts as a neurotransmitter and a neuromodulator and supports cognitive function. It binds to two main types of receptors, nicotinic and muscarinic, that have different properties and mechanisms. There are muscle-type and neuronal-type *nicotinic ACh receptors*; the latter type are located in the autonomic ganglia of the sympathetic and parasympathetic nervous systems (discussed later in this chapter). Nicotine also binds to these receptors and imitates the actions of ACh—hence their name. *Muscarinic ACh receptors* are found in both the central nervous system and in the heart, lungs, upper gastrointestinal tract, and sweat glands. Some ACh receptors have inhibitory effects; others have excitatory effects. In the CNS, the drug nicotine binds to nicotinic acetylcholine receptors to increase arousal, sustain attention, enhance learning and memory, and increase REM sleep.

Many plants and animals produce toxins and venoms that affect ACh levels. For example, botulinum toxin suppresses the release of ACh at the neuromuscular junction, causing flaccid paralysis. Because of this property, Botox, a commercial product containing minuscule amounts of botulinum toxin, is used to relax the muscles in multiple disorders characterized by overactive muscle activity, such as post-stroke spasticity. It is also used for cosmetic purposes, because a small injection into subcutaneous muscles results in reduced wrinkling of the overlying skin in areas such as around the eyes. The plant toxin curare has a different mechanism. It binds to the nicotinic ACh receptor, also decreasing ACh levels, and causing muscle weakness and, in sufficient doses, flaccid paralysis of the diaphragm and death. Some toxins and venoms inhibit the action of the ACh breakdown enzyme acetylcholinesterase (AChE), leading to excess ACh at the neuromuscular junction and resulting in continuous activation of muscles, causing rigid paralysis. In this case, death can be caused by hyperactivity and rigidity of the muscles needed for breathing.

The primary sites of *dopamine* production are the adrenal glands and a few small areas of the brain. Brain areas with significant dopaminergic innervation include the striatum, substantia nigra, and hypothalamus. So far, five different types of dopamine receptors have been identified (with hints of two more), labeled from D_1 to D_5, all of which are G protein–coupled receptors, exerting their effects on postsynaptic neurons via the second-messenger mechanism. There are several dopaminergic pathways, each sprouting from one of the small brain areas where it is produced and each involved in particular functions, including cognitive and motor control, motivation, arousal, reinforcement, and reward, among others. Parkinson's disease, schizophrenia, attention deficit hyperactivity disorder, and addiction are associated with deficits in dopamine systems.

Serotonin in the brain is released largely by the neurons of the raphe nuclei, located in the brainstem. Axons from the raphe nuclei neurons extend to most parts of the central nervous system, forming a neurotransmitter system. Serotonin receptors—both ligand-gated ion channels and GPCRs—are found on the cell membrane of neurons and other cell types that mediate both excitatory and inhibitory neurotransmission. Serotonergic pathways are involved in the regulation of mood, temperature, appetite, behavior, muscle contraction, sleep, and the cardiovascular and endocrine systems. Serotonin also has effects on learning and memory. Drugs such as the selective serotonin reuptake inhibitors (SSRIs), used to treat clinical depression, act on the raphe nuclei and their targets in the brain.

Norepinephrine (NE), also known as *noradrenaline*, is the sympathetic nervous system's go-to neurotransmitter. It is produced and used by neurons with cell bodies in the locus coeruleus (LC), an area of the brain involved with physiological responses to stress and located in one of the brainstem's structures, the pons. These neurons have extensive projections to the cortex, cerebellum, and spinal cord. Activity in the LC is low during sleep, runs at a baseline level during awake periods, steps up the action

when presented with an attention-drawing stimulus, and strongly activates when potential danger is sensed.

Outside the brain, NE is released by the adrenal glands. There are two types of receptors for NE: alpha (α_1 and α_2) and beta (β_1, β_2, and β_3), both of which are GPCRs. Alpha-2 receptors tend to have inhibitory effects, while alpha-1 and the beta receptors tend to have excitatory effects. NE mediates the fight-or-flight response. Its general effect is to prepare the body and its organs for action. It increases arousal, alertness, and vigilance; focuses attention; and enhances memory formation. Along with these effects come increased anxiety and restlessness. The body responds to NE with increased heart rate, blood pressure, and blood flow to skeletal muscles, and decreased blood flow to the gastrointestinal system. It also increases the availability of stored glucose for energy.

Neurosteroids are steroids synthesized in the brain. Only in the last 40 years have researchers found evidence that the brain can synthesize steroids. There are many different neurosteroids, some inhibitory and some excitatory; they can modulate the binding of various neurotransmitters on both directly and indirectly gated receptors and also directly activate GPCRs (reviewed in Do Rego et al., 2009). Neurosteroids are involved with the control of various neurobiological processes, including cognition, stress, anxiety, depression, aggressiveness, body temperature, blood pressure, locomotion, feeding behavior, and sexual behavior.

For example, *estradiol* is a hormone derived from cholesterol (like other steroid hormones) and is produced primarily in the ovaries of women and the testes of men. The brain, however, also has the molecules and enzymes necessary for the conversion of cholesterol into steroids such as estradiol (as well as progesterone and testosterone), and it has specific receptors for each of these neurosteroids and for peripherally produced steroid hormones. Estradiol is a neuroprotective factor, and recent discoveries indicate that neural estrogen receptors coordinate multiple signaling mechanisms that protect the brain from neurodegenerative diseases, affective disorders, and cognitive decline (reviewed in Arevalo et al., 2015).

Inactivation of neurotransmitters after release. Following the release of neurotransmitter into the synaptic cleft and its binding with the postsynaptic membrane receptors, the remaining transmitter must be removed to prevent further excitatory or inhibitory signal transduction. This removal can be accomplished by active reuptake of the substance back into the presynaptic terminal, by enzymatic breakdown of the transmitter in the synaptic cleft, or merely by diffusion of the neurotransmitter away from the region of the synapse or site of action (e.g., in the case of hormones that act on target cells distant from the synaptic terminals).

Neurotransmitters that are removed from the synaptic cleft by reuptake mechanisms include the biogenic amines (dopamine, norepinephrine, epinephrine, histamine, and serotonin). The reuptake mechanism is mediated by active transporters, which are transmembrane proteins that pump the neurotransmitter back across the presynaptic membrane.

An example of a neurotransmitter that is eliminated from the synaptic cleft by enzymatic action is ACh. The enzyme AChE, located in the synaptic cleft, breaks down ACh after it has acted on the postsynaptic membrane. In fact, special AChE stains (chemicals that bind to AChE) can be used to label AChE on muscle cells, thus revealing where motor neurons innervate the muscle.

To monitor the level of neurotransmitter in the synaptic cleft, presynaptic neurons have autoreceptors. These autoreceptors are located on the presynaptic terminal and bind with the released neurotransmitter, enabling the presynaptic neuron to regulate the synthesis and release of the transmitter.

Electrical Transmission

Some neurons communicate via electrical synapses, which are very different from chemical synapses. In electrical synapses, no synaptic cleft separates the neurons. Instead, the neuronal membranes touch at specializations called *gap junctions*, and the cytoplasms of the two neurons are essentially continuous. These gap junction channels create pores connecting the cytoplasms of the two neurons (**Figure 2.16**). As a result, the two neurons are *isopotential* (i.e., they have the same electrical potential), meaning that electrical changes in one are reflected instantaneously in the other. Following the principles of electrotonic conduction, however, the passive currents that flow between the

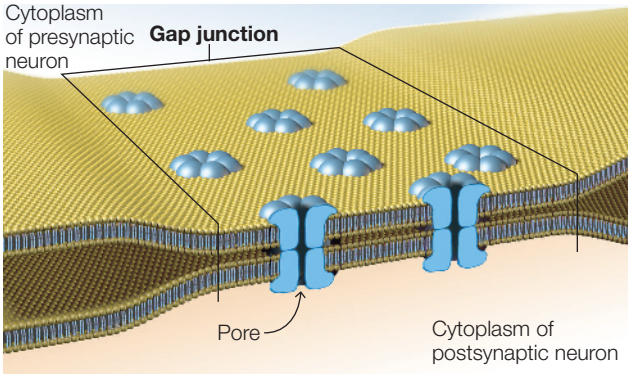


FIGURE 2.16 Electrical synapse between two neurons. Electrical synapses are formed by gap junctions, places where multiple transmembrane proteins in the pre- and postsynaptic neurons connect to create pathways that connect the cytoplasms of the two neurons.

neurons when one of them is depolarized (or hyperpolarized) decrease and are therefore smaller in the postsynaptic neuron than in the presynaptic neuron. Under most circumstances, the communication is bidirectional; however, so-called rectifying synapses limit current flow in one direction, as is typical in chemical synapses.

Electrical synapses are useful when information must be conducted rapidly, such as in the escape reflex of some invertebrates. Groups of neurons with these synapses can activate muscles quickly to get the animal out of harm's way. For example, the well-known tail flip reflex of crayfishes involves powerful rectifying electrical synapses. Electrical synapses are also useful when groups of neurons should operate synchronously, as with some hypothalamic neurosecretory neurons. Electrical synapses also have some limitations: They are much less plastic than chemical synapses, and they cannot amplify a signal (whereas an action potential that triggers a chemical synapse could cause a large release of neurotransmitter, thus amplifying the signal).

TAKE-HOME MESSAGES

- Synapses are the locations where one neuron can transfer information to another neuron or a specialized nonneuronal cell. They are found on dendrites and at axon terminals but can also be found on the neuronal cell body.
- Chemical transmission results in the release of neurotransmitters from the presynaptic neuron and the binding of those neurotransmitters on the postsynaptic neuron, which in turn causes excitatory or inhibitory postsynaptic potentials (EPSPs or IPSPs), depending on the properties of the postsynaptic receptor.
- Neurotransmitters must be removed from the receptor after binding. This removal can be accomplished by active reuptake back into the presynaptic terminal, enzymatic breakdown of the transmitter in the synaptic cleft, or diffusion of the neurotransmitter away from the region of the synapse.
- Electrical synapses are different from chemical synapses because they operate by passing current directly from one neuron (presynaptic) to another neuron (postsynaptic) via specialized channels in gap junctions that connect the cytoplasm of one cell directly to the other.

2.3 Overview of Nervous System Structure

Until now, we have been talking about only one or two neurons at a time. This approach is useful in understanding how neurons transmit information, but it is only one part of how the nervous system and the brain function. Neural communication depends on patterns of connectivity in the nervous system, the neural "highways" along which information travels from one place to another. Identifying patterns of connectivity in the nervous system is tricky because most neurons are not wired together in simple, serial circuits. Instead, neurons are extensively connected in both serial and parallel circuits.

A single cortical neuron is likely to be innervated by (i.e., receive inputs from) a large number of neurons: A typical cortical neuron has between 1,000 and 5,000 synapses, while a Purkinje neuron in the cerebellum may have up to 200,000 synapses. The axons from these input neurons can originate in widely distributed regions. Thus, there is tremendous convergence in the nervous system, but also divergence, in which a single neuron can project to multiple target neurons in different regions.

Localized interconnected neurons form what is known as a **microcircuit**. They process specific kinds of information and can accomplish sophisticated tasks such as processing sensory information, generating movements, and mediating learning and memory. For example, microcircuits in the retina of the eye process information from small regions of visual space. The patterns of light entering the eye strike photoreceptors, and the information from adjacent photoreceptors is processed through the microcircuitry of the retina to encode spatial information. This encoding permits a much smaller number of retinal ganglion cells to transmit the coded information down the optic nerve.

Although most axons are short projections from neighboring cortical cells, some are quite long, originating in one region of the brain and projecting to another at some distance. For example, the ganglion cells of the retina project via the optic nerve to the lateral geniculate nucleus of the thalamus, and the lateral geniculate neurons project via the optic radiations to primary visual cortex. Axons from neurons in the cortex may reach distant targets by descending below the cortical sheath into the white matter, traveling through long fiber tracts, and then entering another region of cortex, subcortical nucleus, or spinal layer to synapse on another neuron.

These long-distance connections between various brain regions connect to form more complex **neural networks**, which are *macro*circuits that are made up of multiple embedded microcircuits. Neural networks support more complex analyses, integrating information processing from many microcircuits. Connections between two cortical regions are referred to as *corticocortical* connections, following the convention that the first part of the term identifies the source and the second part identifies the target.

Inputs that originate in subcortical structures such as the thalamus would be referred to as *thalamocortical* connections; the reverse are *corticothalamic* or, more generally, *corticofugal* projections (projections extending from more central structures, like cortex, outward toward the peripheral nervous system).

Ultimately, neural networks are organized into neural systems. So, for example, the microcircuits of the retina, the lateral geniculate nucleus of the thalamus, and the patches of visual cortex are organized to create neural networks such as the thalamocortical network. This progression ultimately leads to the organization of the visual system as a whole, with its numerous cortical areas and subcortical components. (We will discuss the organization of the visual system in detail in Chapter 5.) In the next section we go on a brief anatomical tour of the brain. Early in each of Chapters 4 through 14, a section highlights the anatomy most relevant to the cognitive functions discussed in that chapter. The anatomy presented here and in the coming chapters will help you see which structures of the brain are related to which of its functions.

The two main divisions of the nervous system are the **central nervous system (CNS)**, consisting of the brain and spinal cord, and the **peripheral nervous system (PNS)**, consisting of the nerves (bundles of axons and glial cells) and ganglia (clumps of nerve cell bodies) outside of the CNS (**Figure 2.17**). The CNS can be thought of as the command-and-control center of the nervous system. The PNS represents a courier network that delivers sensory information to the CNS and carries motor commands from the CNS to the muscles. These activities are accomplished through two subsystems: the *somatic motor system* that controls the voluntary muscles of the body, and the *autonomic motor system* that controls the automated visceral functions. Before we concentrate on the CNS, a word about the autonomic nervous system.

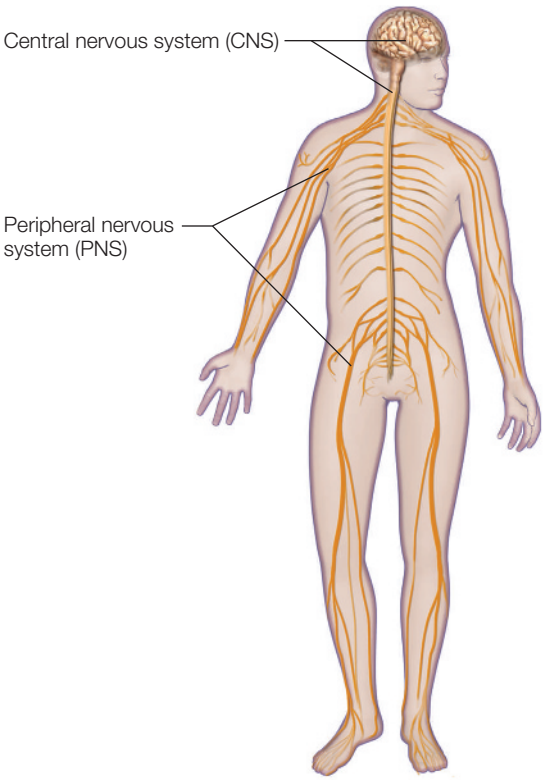


FIGURE 2.17 The peripheral and central nervous systems of the human body.
The nervous system is generally divided into two main parts. The central nervous system (CNS) includes the brain and spinal cord. The peripheral nervous system (PNS), comprising the sensory and motor nerves and associated nerve cell ganglia (groups of neuronal cell bodies), is located outside the central nervous system.

The Autonomic Nervous System

The **autonomic nervous system** (also called the *autonomic motor system* or *visceral motor system*) is involved in controlling the involuntary action of smooth muscles, the heart, and various glands. It also has two subdivisions: the *sympathetic* and *parasympathetic* branches (**Figure 2.18**). In general, the sympathetic system uses the neurotransmitter norepinephrine, and the parasympathetic system uses acetylcholine as its transmitter. The two systems frequently operate antagonistically. For example, activation of the sympathetic system increases heart rate, diverts blood from the digestive tract to the somatic musculature, and prepares the body for action (fight or flight) by stimulating the adrenal glands to release adrenaline. In contrast, activation of the parasympathetic system slows heart rate, stimulates digestion, and in general helps the body with functions germane to maintaining itself (rest and digest).

In the autonomic system, a great deal of specialization takes place that is beyond the scope of this chapter. Still, understanding that the autonomic system is involved in a variety of reflex and involuntary behaviors (mostly below the level of consciousness) is useful for interpreting information presented later in the book. In Chapter 10, on emotion, we will discuss arousal of the autonomic nervous system and how changes in a number of psychophysiological measures tap into emotion-related changes in the autonomic nervous system. For example, changes in skin conductance are related to sweat gland activity, and sweat glands are under the control of the autonomic nervous system.

In the rest of this chapter we focus on the CNS in order to lay the groundwork for the studies of cognition

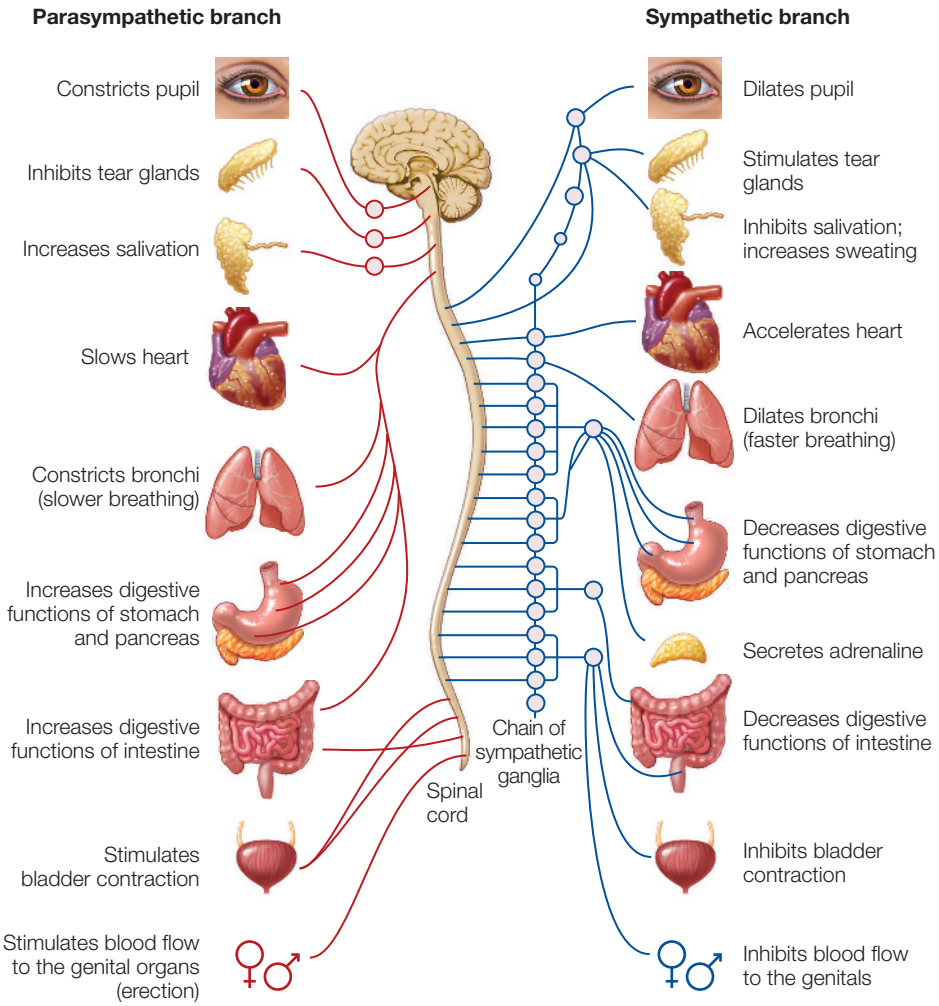


FIGURE 2.18 Organization of the autonomic nervous system.

presented throughout the rest of the book. When we talk about brain anatomy, we will use standard terminology to locate parts of the brain in three-dimensional space (see **Box 2.1**).

The Central Nervous System

The CNS is made up of the brain and spinal cord, and each is covered with three protective membranes, the *meninges.* The outer membrane is the thick dura mater; the middle is the arachnoid mater; and the inner and most delicate is the pia mater, which firmly adheres to the surface of the brain. Between the arachnoid membrane and the pia mater is the subarachnoid space, which is filled with *cerebrospinal fluid (CSF)*, as are the brain's ventricles, cisterns, and sulci, along with the central canal of the spinal cord. The brain actually floats in the CSF, which offsets the pressure and damage that would be present if it were merely sitting and scraping on the base of the skull. CSF also reduces shock to the brain and spinal cord during rapid accelerations or decelerations, such as when we fall, ride roller coasters, or are struck on the head.

Within the brain are four large interconnected cavities called **ventricles** (**Figure 2.19**). The largest are the two lateral ventricles in the cerebrum, which are connected to the more caudal third ventricle in the brain's midline and the fourth ventricle in the brainstem below the cerebellum. The walls of the ventricles contain a system of specialized cells and capillaries, the *choroid plexus*, which produces CSF from blood plasma. The CSF circulates through the ventricles and on to either the subarachnoid space surrounding the brain or the spinal canal. It is reabsorbed in the brain by the *arachnoid villi*, protrusions into the venous system in the sagittal sinus.

In the CNS, neurons are bunched together in various ways (**Figure 2.20**). Two of the most common organizational clusters are the **nucleus** and the **layer**. A nucleus is a relatively compact arrangement of nerve cell bodies

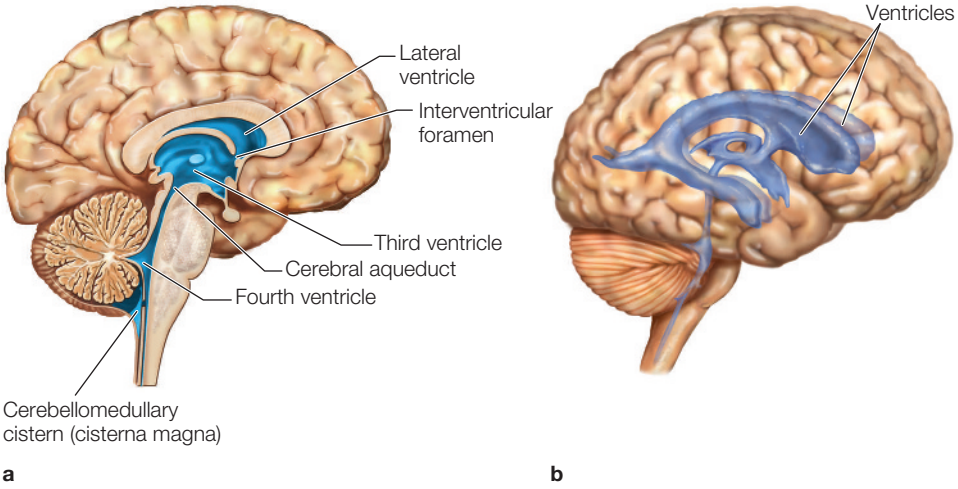


FIGURE 2.19 Ventricles of the human brain.
(a) Midsagittal section, showing the medial surface of the left hemisphere. (b) Transparent brain, showing the ventricular system in 3-D view.

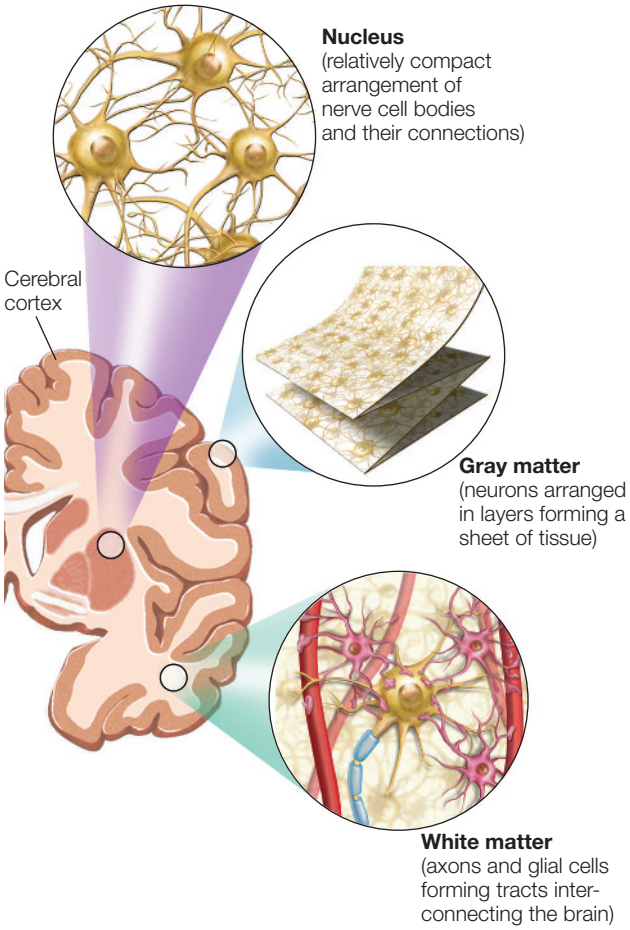


FIGURE 2.20 Organization of neurons in the CNS.
In the CNS, neurons can be organized in clumps called nuclei (top—not to be confused with the nucleus inside each neuron), which are most commonly found in subcortical and spinal structures, or sheets called layers (middle), which are most commonly found in the cortex. The cell bodies of glial cells are located in the white matter (bottom—e.g., oligodendrocytes), and in the cortex.

and their connections, ranging in size from hundreds to millions of neurons with functionally similar inputs and outputs. Nuclei are located throughout both the brain and the spinal cord.

The **cerebral cortex** of the brain, on the other hand, has billions of neurons. They are arranged in a sheet containing several layers of neurons, folded across the surfaces of the cerebral hemispheres like a handkerchief. When we look at a slice of the brain, we see the cerebral cortex as a thin grayish layer overlying a whitish interior. The **cerebellum** is the other structure of the brain that is highly layered, containing billions of neurons, also having gray and white regions. The **gray matter** in these layers is composed of neuronal cell bodies, whereas the **white matter** consists of axons and glial cells.

Much like nerves in the PNS, the axons forming the white matter are grouped together in **tracts** that run from one cortical region to another within a hemisphere (*association tracts*), or that run to and from the cerebral cortex to the deeper subcortical structures and the spinal cord (*projection tracts*). Finally, axons may project from one cerebral hemisphere to the other in bundles that are called **commissures**. The largest of these interhemispheric projections is the main commissure crossing between the hemispheres, the **corpus callosum**.

Blood Supply and the Brain

The brain needs energy and oxygen, which it extracts from blood. Approximately 20% of the blood flowing from the heart is pumped to the brain. A constant flow of blood is necessary because the brain has no way of storing glucose or extracting energy without oxygen. If the flow of oxygenated blood to the brain is disrupted for even a few minutes, unconsciousness and death can result.

BOX 2.1 | THE COGNITIVE NEUROSCIENTIST'S TOOLKIT

Navigating the Brain

For anatomists, the head is merely an appendage of the body, so the terms used to describe the orientation of the head and its brain are in relation to the body. Confusion arises because of differences in how the head and body are arranged in animals that walk on four legs versus humans, who are upright. Let's first picture the body of the cutest kind of dog, an Australian shepherd, looking off to the left of the page (**Figure 2.21a**). The front end is the *rostral* end, meaning "nose." The opposite end is the *caudal* end, the "tail." Along the dog's back is the *dorsal* surface, just as the dorsal fin is on the back of a shark. The bottom surface along the dog's belly is the *ventral* surface.

We can use the same coordinates to describe the dog's nervous system (**Figure 2.21b**). The part of the brain toward the front is the rostral end (toward the frontal lobes); the posterior end is the caudal end (toward the occipital lobe). Along the top of the dog's head is the dorsal surface, and the bottom surface of the brain is the ventral surface.

We humans are atypical animals because we stand upright and therefore tilt our heads forward in order to be parallel with the ground. Thus, the dorsal surfaces of the human body and brain are at right angles to each other (**Figure 2.22**). In humans, we also use the terms *superior* to refer to the dorsal surface of the brain and *inferior* to refer to the ventral surface of the brain. Similarly, the terms *anterior* and *posterior* are used to refer to the front (rostral) and back (caudal) ends of the brain, respectively (Figure 2.22b). When we consider the spinal cord, the coordinate systems

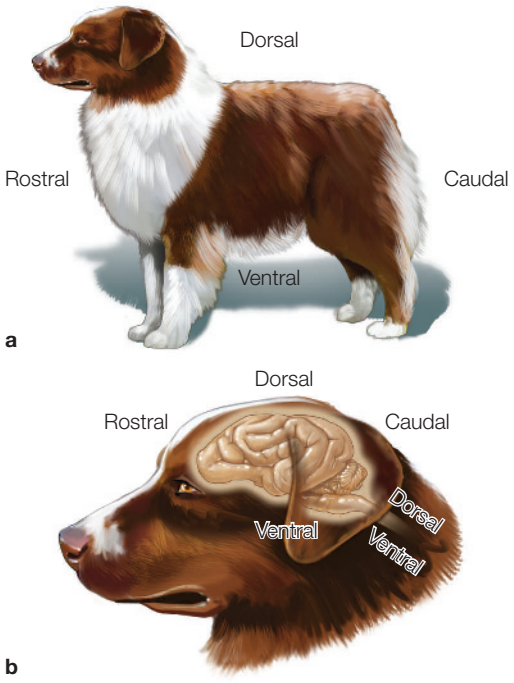


FIGURE 2.21 A dog brain in relation to the body.

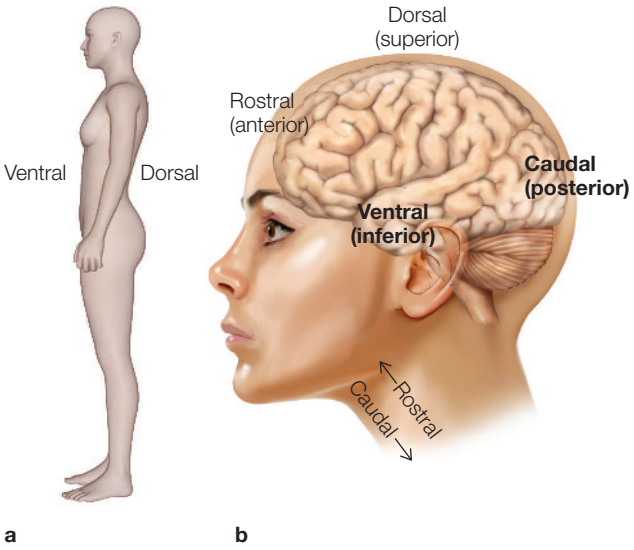


FIGURE 2.22 Navigating the human brain.

align with the body axis. Thus, in the spinal cord *rostral* means "toward the brain," just as it does in the dog.

Throughout this book, pictures of brain slices are usually in one of three planes (**Figure 2.23**). If we slice the brain from nose to tail, we get a *sagittal* section. When we slice directly through the middle, we get a *midsagittal* or *medial* section. If we slice off to the side, we get a *lateral sagittal* section. If we slice perpendicular to a midsagittal section, separating the front of the brain from the back, we get a *coronal* section. When we slice in a plane that separates dorsal from ventral, we get a section that is described as *axial*, *transverse*, or *horizontal*.

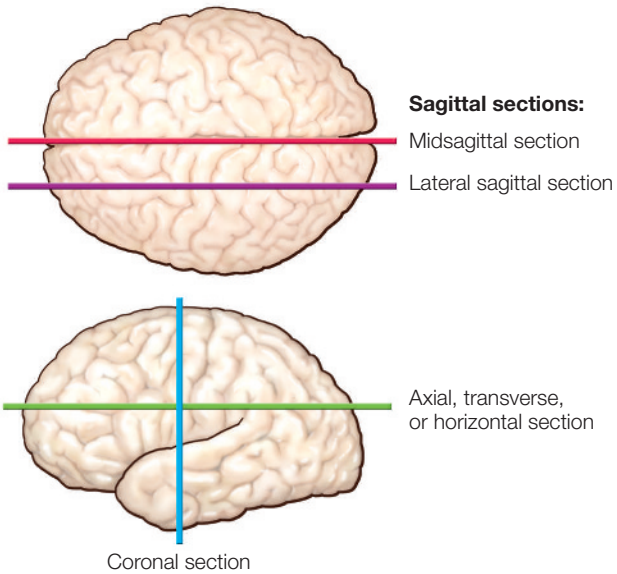
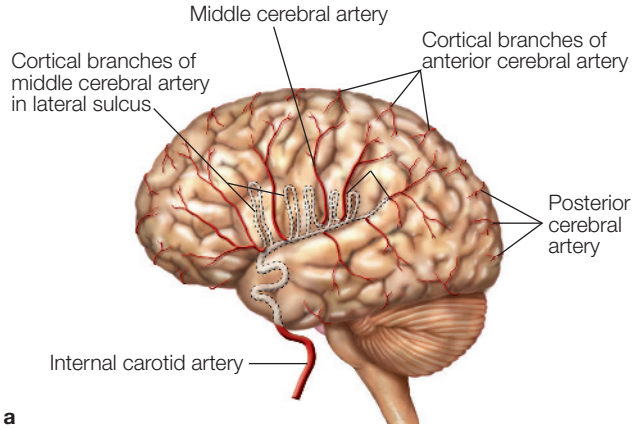
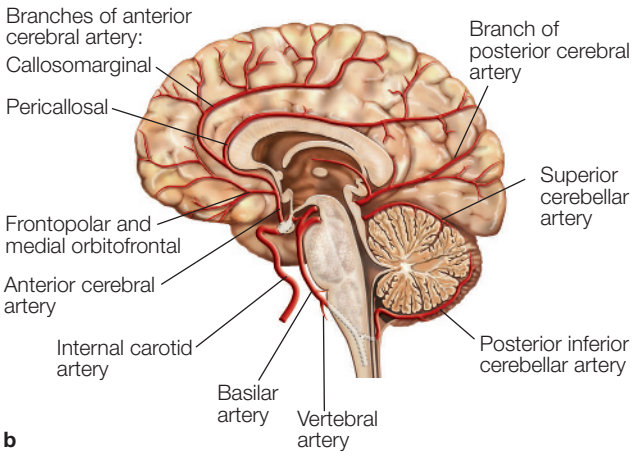


FIGURE 2.23 Three types of orthogonal planes through the brain.





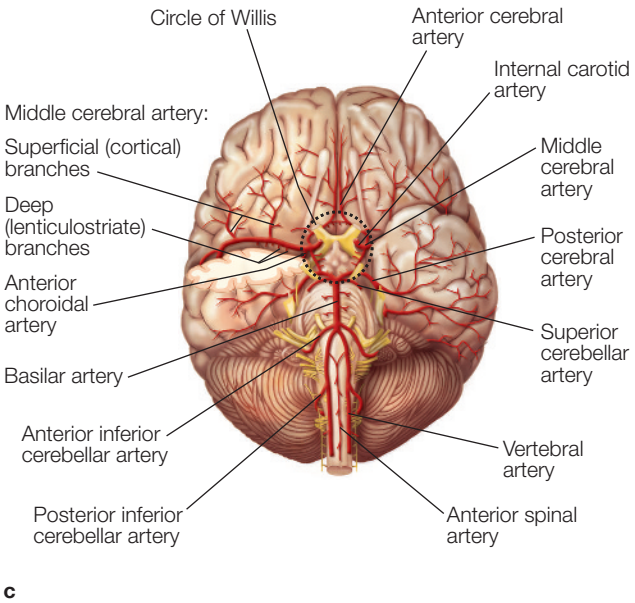


FIGURE 2.24 Blood supply and the brain.
(a) Blood supply to the lateral aspect of the cortex. (b) The midsagittal section reveals branches of the anterior cerebral artery, which extend from the anterior aspect of the circle of Willis and a portion of the posterior cerebral artery, which extends from the posterior aspect of the circle of Willis. (c) Ventral view of brain, showing the circle of Willis, the arteries encircling the base of the brain. The circle of Willis is supplied with arterial blood from the right and left internal carotid arteries, which extend the right and left common carotid artery and the basilar artery formed by the right and left vertebral arteries, which are branches of the subclavian artery.

Two sets of arteries bring blood to the brain: the vertebral arteries, which supply blood to the caudal portion of the brain, and the internal carotid arteries, which supply blood to wider brain regions (**Figure 2.24**). Although the major arteries sometimes join together and then separate again, little mixing of blood occurs between the rostral and caudal arterial supplies or between the right and left sides of the rostral portion of the brain. As a safety measure, in the event of a blockage or ischemic attack, the circulatory system can reroute blood to reduce the probability of a disruption in blood supply; in practice, however, this rerouting of the blood supply is relatively poor.

Blood flow in the brain is tightly coupled with metabolic demand of the local neurons. Hence, increases in neuronal activity lead to a coupled increase in regional cerebral blood flow. The primary purpose of increased blood flow is not to increase the delivery of oxygen and glucose to the active tissue, but rather to hasten removal of the resultant metabolic by-products of the increased neuronal activity. The precise mechanisms for altering blood flow, however, remain hotly debated. These local changes in blood flow permit regional cerebral blood flow to be used as a measure of local changes in neuronal activity, serving as the basis for some types of functional neuroimaging, such as positron emission tomography and functional magnetic resonance imaging.

TAKE-HOME MESSAGES

- The central nervous system consists of the brain and spinal cord. The peripheral nervous system consists of all nerves and neurons outside of the central nervous system.
- The autonomic nervous system is involved in controlling the action of smooth muscles, the heart, and various glands. Its sympathetic branch, when activated, increases heart rate, diverts blood from the digestive tract to the somatic musculature, and prepares the body for fight-or-flight responses by stimulating the adrenal glands. Its parasympathetic branch is responsible for decreasing heart rate and stimulating digestion.
- The cerebral cortex is a continuous sheet of layered neurons on the surface of each cerebral hemisphere.
- The axons of cortical neurons and subcortical ganglia travel together in white matter tracts that interconnect neurons in different parts of the brain and spinal cord. Bundles of axons that cross from one cerebral hemisphere to the other are known as commissures. The corpus callosum is the largest commissure connecting the two hemispheres of the brain.

2.4 A Guided Tour of the Brain

When we see a brain, the cerebral cortex, the outer layer, is most prominent. Yet the cerebral cortex is just the frosting on the cake; it's the last thing to develop from an evolutionary, as well as an embryological, point of view. Deep within, at the base of the brain, are structures that are found in most vertebrates and have been evolving for hundreds of millions of years. These parts of the brain control our most basic survival functions, such as breathing, heart rate, and temperature. In contrast, the prefrontal cortex, which is found only in mammals, is the evolutionarily youngest part of the brain. Damage to the prefrontal cortex may not be immediately fatal, but it will likely affect such things as our ability to make decisions and to control our social behavior. We begin our tour of the CNS with a brief look at the spinal cord, and we will work our way up to the cortex.

The Spinal Cord

The spinal cord takes in sensory information from the body's peripheral sensory receptors, relays it to the brain, and conducts the outgoing motor signals from the brain to the muscles. In addition, each level (segment) of the spinal cord has monosynaptic reflex pathways that involve synapses only in the spinal cord itself, and not in the brain. For example, a tap by your doctor on your patellar tendon at the knee sends a sensory signal to the spinal cord that, via interneurons, directly stimulates motor neurons to fire action potentials leading to muscle contraction and the resultant brief knee jerk. This is an example of a monosynaptic reflex arc (**Figure 2.25**). Most neural circuits, however, process information through more than a single synapse.

The spinal cord runs from the brainstem at about the first spinal vertebra to its termination in the *cauda equina* (meaning "horse's tail"). It is enclosed in the bony *vertebral column*—a stack of separate bones, the *vertebrae*, that extend from the base of the skull to the fused vertebrae at the *coccyx* (tailbone). The vertebral column is divided into sections: cervical, thoracic, lumbar, sacral, and coccygeal. The spinal cord is similarly divided (excluding the coccygeal region, since we no longer have tails) into 31 segments. Each segment has a right and a left *spinal nerve* that enters and exits from the vertebral column through openings called *foramina* (singular *foramen*). Each spinal nerve has both sensory and motor axons: the afferent neuron carries sensory input through the dorsal root into the spinal cord, and the efferent neuron carries motor output through the ventral root away from the spinal cord.

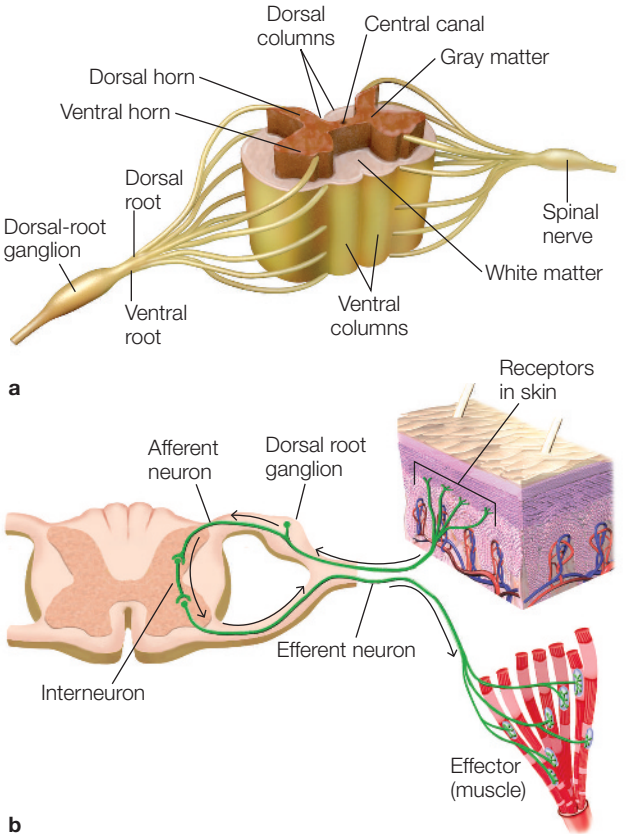


FIGURE 2.25 Gross anatomy of the spinal cord and reflex arc. This cross-sectional 3-D representation of the spinal cord **(a)** shows the central butterfly-shaped gray matter (which contains neuronal cell bodies) and the surrounding white matter axon tracts (which convey information down the spinal cord from the brain to the peripheral neurons and up the spinal cord from peripheral receptors to the brain). The cell bodies of peripheral sensory inputs reside in the dorsal-root ganglion and project their axons into the central nervous system via the dorsal root. The ventral horn of the spinal cord houses motor neurons that project their axons out the ventral roots to innervate peripheral muscles. The dorsal and ventral roots fuse to form peripheral nerves. The interneurons directly connect the afferent sensory nerves to the efferent motor nerves, forming a neural circuit that mediates spinal cord reflexes such as the knee jerk **(b)**.

As the cross section of the spinal cord in Figure 2.25 shows, the peripheral region is made up of white matter tracts. The more centrally located gray matter, consisting of neuronal cell bodies, resembles a butterfly with two separate sections, or "horns": the *dorsal horn* and the *ventral horn*. The ventral horn contains the large motor neurons that project to muscles. The dorsal horn contains sensory neurons and interneurons. The interneurons project to motor neurons on the same (*ipsilateral*) and opposite (*contralateral*) sides of the spinal cord to aid in the coordination of limb movements. They also form local circuits between ipsilateral sensory and motor nerves that mediate spinal reflexes. The gray matter surrounds the *central canal*, which is an anatomical extension of the ventricles in the brain and contains cerebrospinal fluid.

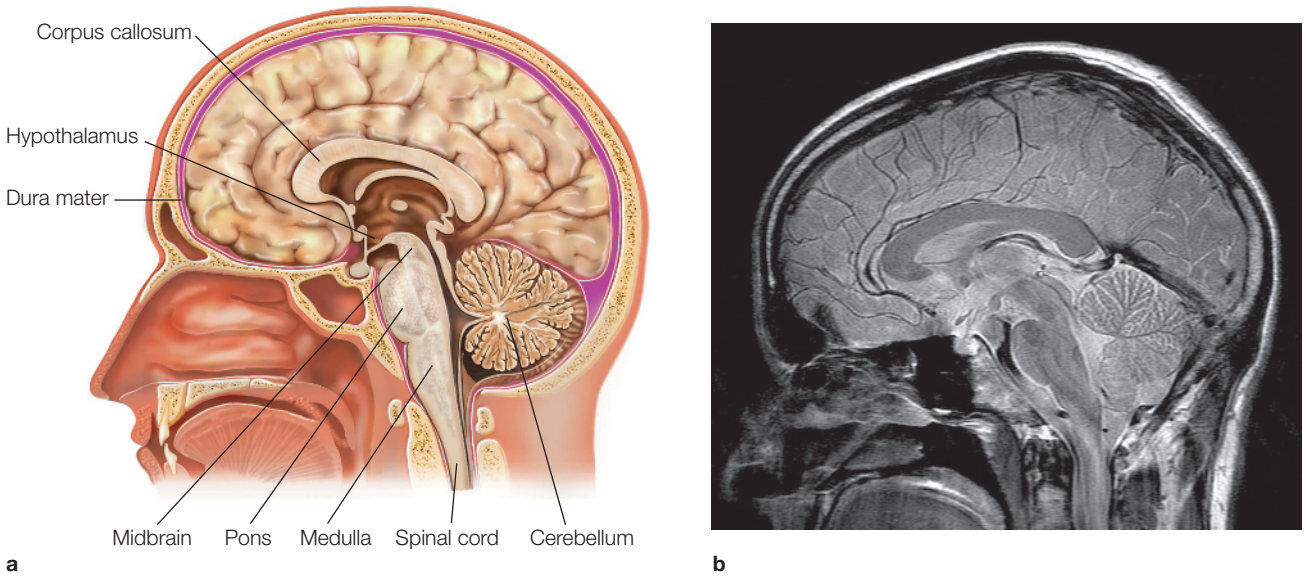


FIGURE 2.26 Gross anatomy of a brain, showing the brainstem.
(a) Midsagittal section through the head, showing the brainstem, cerebellum, and spinal cord. **(b)** High-resolution structural MRI obtained with a 4-tesla scanner, showing the same plane of section as in (a).

The Brainstem: Medulla, Pons, Cerebellum, and Midbrain

We usually think of the **brainstem** as having three main parts: the medulla (myelencephalon), the pons and cerebellum (metencephalon), and the midbrain (mesencephalon). These three sections form the central nervous system between the spinal cord and the diencephalon. The brainstem contains groups of motor and sensory nuclei, nuclei of widespread modulatory neurotransmitter systems, and white matter tracts of ascending sensory information and descending motor signals. Though it is rather small compared to the vast bulk of the forebrain (**Figure 2.26**), the brainstem plays a starring role: Damage to the brainstem is life-threatening, largely because brainstem nuclei control respiration and global states of consciousness such as sleep and wakefulness.

The medulla, pons, and cerebellum make up the hindbrain, which we look at next.

MEDULLA The brainstem's most caudal portion is the **medulla**, which is continuous with the spinal cord (**Figure 2.27**). The medulla is essential for life. It houses the cell bodies of many of the 12 cranial nerves, providing sensory and motor innervations to the face, neck, abdomen, and throat (including taste), as well as the motor nuclei that innervate the heart. The medulla controls vital functions such as respiration, heart rate, and arousal.

All of the ascending somatosensory information entering from the spinal cord passes through the medulla via two bilateral nuclear groups, the *gracile* and *cuneate nuclei.*

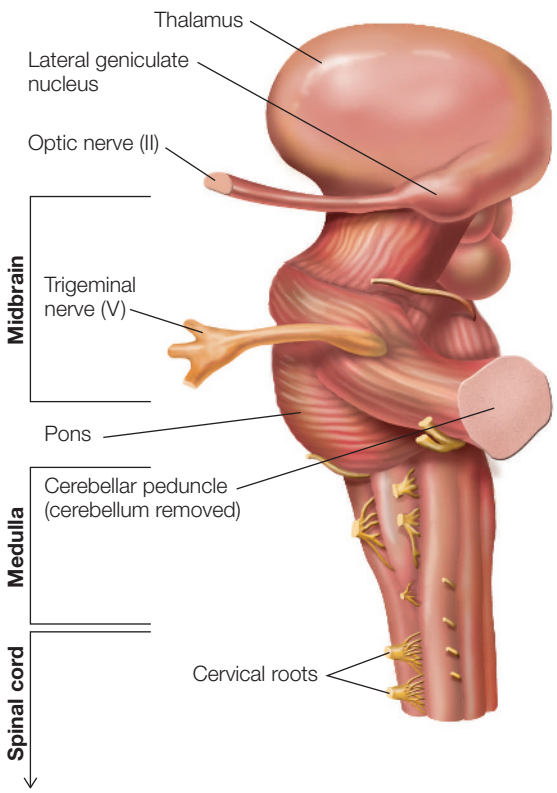


FIGURE 2.27 Lateral view of the brainstem, showing the thalamus, pons, medulla, midbrain, and spinal cord.
In this left lateral view of the brainstem, the top is the anterior portion of the brain, and the spinal cord is toward the bottom. The cerebellum is removed in this drawing.

These projection systems continue through the brainstem to synapse in the thalamus en route to the somatosensory cortex. Another interesting feature of the medulla is that the corticospinal motor axons, tightly packed in a pyramid-shaped bundle (called the *pyramidal tract*), cross here to form the *pyramidal decussation*. Thus, the motor neurons originating in the right hemisphere cross to control muscles on the left side of the body, and vice versa.

Functionally, the medulla is a relay station for sensory and motor information between the body and brain; it is the crossroads for most of the body's motor fibers; it controls several autonomic functions, including the essential reflexes that determine respiration, heart rate, blood pressure, and digestive and vomiting responses.

PONS The **pons**, Latin for "bridge," is so named because it is the main connection between the brain and the cerebellum. Sitting anterior to the medulla, the pons is made up of a vast system of fiber tracts interspersed with nuclei (Figure 2.27). Many of the cranial nerves synapse in the pons, including the sensory and motor nuclei from the face and mouth, and the visuomotor nuclei controlling some of the extraocular muscles. Thus, the pons is important for some eye movements, as well as movements of the face and mouth. In addition, some auditory information is channeled through another pontine structure, the superior olive.

This level of the brainstem contains a large portion of the reticular formation, a set of interconnected nuclei located throughout the brainstem that modulate arousal and pain, and that have various other functions, including cardiovascular control. The reticular formation has three columns of nuclei: the *raphe nuclei*, where the brain's serotonin is synthesized; the *parvocellular reticular nuclei*, which regulate exhalation; and the *gigantocellular nuclei*, which help to regulate cardiovascular functions. Interestingly, the pons is also responsible for generating rapid eye movement (REM) sleep.

CEREBELLUM The cerebellum (literally, "small cerebrum" or "little brain") clings to the brainstem at the level of the pons (Figure 2.26a). It is—perhaps surprisingly, given its size—home to most of the brain's neurons, estimated at 69 billion of the 89 billion neurons we have. Visually, the surface of the cerebellum appears to be covered with thinly spaced, parallel grooves, but in reality it is a continuous layer of tightly folded neural tissue (like an accordion). It forms the roof of the fourth ventricle and sits on the cerebellar *peduncles* (meaning "feet"), which are massive input and output fiber tracts of the cerebellum (Figure 2.27). The cerebellum has several gross subdivisions, including the cerebellar cortex, four pairs of deep nuclei (**Figure 2.28**), and the internal white matter. In this way, the cerebellum resembles the forebrain's cerebral hemispheres.

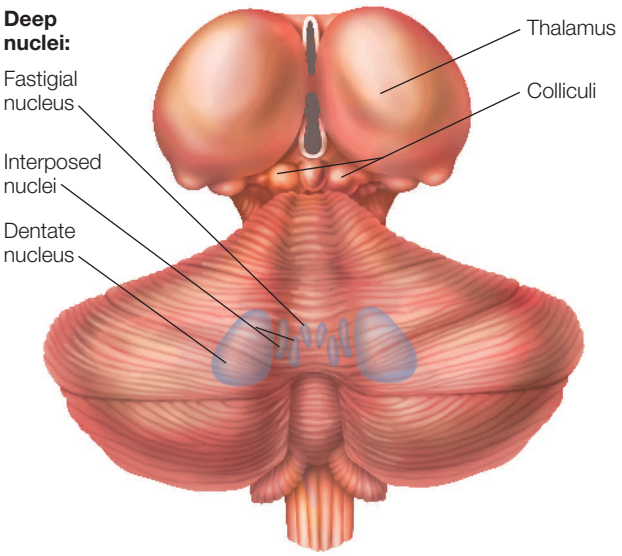


FIGURE 2.28 Gross anatomy of the cerebellum.
In this view, the top is toward the anterior of the brain, and the spinal cord is toward the bottom (not shown). This dorsal view of the cerebellum shows the underlying deep nuclei in a see-through projection—the fastigial nucleus, the dentate nucleus, and the interposed nuclei, which are made up of two fused nuclei: the emboliform and globose nuclei.

Most of the fibers arriving at the cerebellum project to the cerebellar cortex, conveying information about motor outputs and sensory inputs describing body position. Inputs from vestibular projections involved in balance, as well as auditory and visual inputs, also project to the cerebellum from the brainstem. The output from the cerebellum originates in the deep nuclei. Ascending outputs travel to the thalamus and then to the motor and premotor cortex. Other outputs project to nuclei of the brainstem, where they impinge on descending projections to the spinal cord.

The cerebellum is critical for maintaining posture, walking, and performing coordinated movements. It does not directly control movements; instead, it integrates information about the body, such as its size and speed, with motor commands. Then it modifies motor outflow to effect smooth, coordinated movements. The cerebellum is the reason why Yo-Yo Ma can play the cello and the Harlem Globetrotters can dunk a ball with such panache. If your cerebellum is damaged, your movements will be uncoordinated and halting, and you may not be able to maintain balance. In Chapter 8 we look more closely at the cerebellum's role in motor control. In the 1990s, it was discovered that the cerebellum is involved with more than motor functions. It has been implicated in aspects of cognitive processing including language, attention, learning, and mental imagery.

MIDBRAIN The mesencephalon, or **midbrain**, lies superior to the pons and can be seen only in a medial view. It surrounds the cerebral aqueduct, which connects the third and fourth ventricles. Its dorsal portion consists of the *tectum* (meaning "roof"), and its ventral portion is the *tegmentum* ("covering"). The thin layer of gray matter immediately surrounding the cerebral aqueduct within the tegmentum is the *periaqueductal gray*, which hosts a hub of activity that integrates incoming threatening stimuli and outputs processing to shape behavior. The periaqueductal gray receives pain fibers ascending from the spinal cord on their way to the thalamus and is key to the modulation of descending pain signals. Along with multiple other roles, it is involved with the processing of anxiety and fear and is critical for autonomic regulation and for defensive responses.

Large fiber tracts course through the midbrain's ventral regions from the forebrain to the spinal cord, cerebellum, and other parts of the brainstem. The midbrain also contains some of the cranial nerve ganglia and two other important structures: the superior and inferior colliculi (**Figure 2.29**). The *superior colliculus* plays a role in perceiving objects in the periphery and orienting our gaze directly toward them, bringing them into sharper view. The *inferior colliculus* is used for locating and orienting toward auditory stimuli. Another structure, the *red nucleus*, is involved in certain aspects of motor coordination. It helps a baby crawl or coordinates the swing of your arms as you walk. Much of the midbrain is occupied by the mesencephalic reticular formation, a rostral continuation of the pontine and medullary reticular formation, which contains nuclei that have neurotransmitters like norepinephrine and serotonin, touched on earlier.

The Diencephalon: Thalamus and Hypothalamus

After leaving the brainstem, we arrive at the diencephalon, which is made up of the thalamus and hypothalamus. These subcortical structures are composed of groups of nuclei with interconnections to widespread brain areas.

THALAMUS Almost exactly in the center of the brain and perched on top of the brainstem (at the anterior end; Figure 2.27), the **thalamus** is the larger of the diencephalon structures. The thalamus is divided into two parts—one in the right hemisphere and one in the left—that straddle the third ventricle. In most people, the two parts are connected by a bridge of gray matter called the *massa intermedia* (Figure 2.29). Above the thalamus are the fornix and corpus callosum; beside it is the *internal capsule*, containing ascending and descending axons running between the cerebral cortex and the medulla and spinal cord.

The thalamus has been referred to as the "gateway to the cortex" because, except for some olfactory inputs, all of the sensory modalities make synaptic relays in the thalamus before continuing to the primary cortical sensory receiving areas (**Figure 2.30**). The thalamus also receives inputs from the basal ganglia, cerebellum, neocortex, and

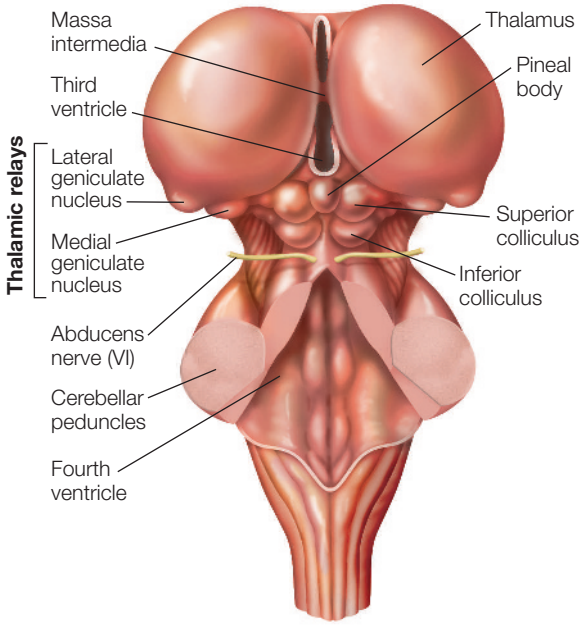


FIGURE 2.29 Anatomy of the midbrain.
The dorsal surface of the brainstem is shown with the cerebral cortex and cerebellum removed.

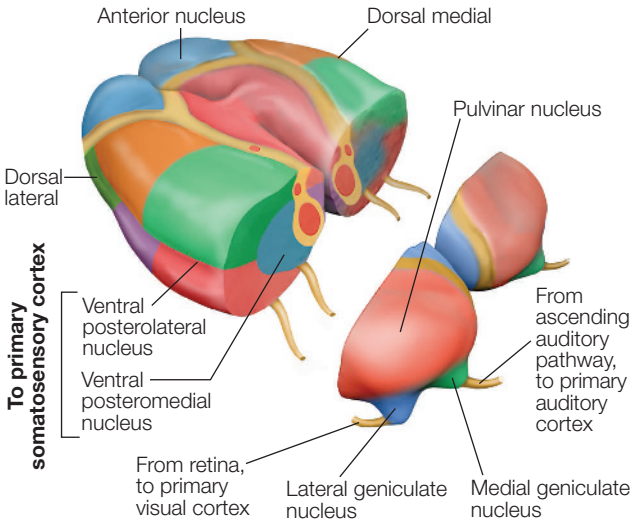


FIGURE 2.30 The thalamus, showing inputs and outputs and major subdivisions.
The various subdivisions of the thalamus serve different sensory systems and participate in various cortical–subcortical circuits. The posterior portion of the thalamus (lower right) is cut away in cross section and separated from the rest of the thalamus to reveal the internal organization of the thalamic nuclei (on the left).

medial temporal lobe, and sends projections back to these structures to create circuits involved in many different functions. Thus, the thalamus, a veritable Grand Central Station of the brain, is considered a relay center where neurons from one part of the nervous system synapse on neurons that travel to another region.

The thalamus is divided into several nuclei that act as specific relays for incoming sensory information. The *lateral geniculate nucleus* receives information from the ganglion cells of the retina and sends axons to the primary visual cortex. Similarly, the *medial geniculate nucleus* receives information from the inner ear, via other brainstem nuclei in the ascending auditory pathway, and sends axons to the primary auditory cortex. Somatosensory information projects via the *ventral posterior (medial and lateral) nuclei of the thalamus* to the primary somatosensory cortex. Sensory relay nuclei of the thalamus not only project axons to the cortex, but also receive heavy descending projections back from the same cortical area that they contact. Located at the posterior pole of the thalamus is the *pulvinar nucleus*, which is involved in attention and in integrative functions involving multiple cortical areas.

HYPOTHALAMUS The main link between the nervous system and the endocrine system is the **hypothalamus**, which is the chief site for hormone production and control. Easily located, the hypothalamus lies on the floor of the third ventricle (Figure 2.26a). The two bumps seen on the ventral surface of the brain, the *mammillary bodies*, belong to the small collection of nuclei and fiber tracts contained in the hypothalamus (**Figure 2.31**). The hypothalamus receives inputs from limbic system structures and other brain areas. One of its jobs is to control circadian rhythms (light–dark cycles) with inputs from the mesencephalic reticular formation, amygdala, and retina. Extending from the hypothalamus are major projections to the prefrontal cortex, amygdala, spinal cord, and pituitary gland. The pituitary gland is attached to the base of the hypothalamus.

The hypothalamus controls the functions necessary for maintaining the normal state of the body (homeostasis): basal temperature and metabolic rate, glucose and electrolyte levels, hormonal state, sexual phase, circadian cycles, and immunoregulation. It sends out signals that drive behavior to alleviate such feelings as thirst, hunger, and fatigue. It accomplishes much of this work through the endocrine system via control of the **pituitary gland**.

The hypothalamus produces hormones, as well as factors that regulate hormone production in other parts of the brain. For example, hypothalamic neurons send axonal projections to the *median eminence*, an area bordering the pituitary gland that releases regulatory hormones

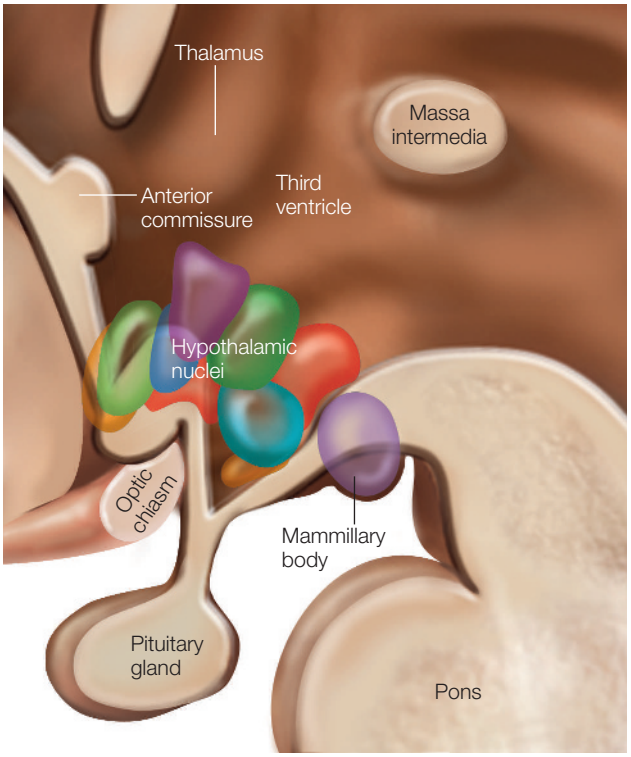


FIGURE 2.31 Midsagittal view of the hypothalamus. Various nuclear groups are shown diagrammatically. The hypothalamus is the floor of the third ventricle and, as the name suggests, sits below the thalamus. Anterior is to the left in this drawing.

into the circulatory system of the anterior pituitary gland. These in turn trigger (or inhibit) the release of a variety of hormones from the anterior pituitary into the bloodstream, such as growth hormone, thyroid-stimulating hormone, adrenocorticotropic hormone, and the gonadotropic hormones.

Hypothalamic neurons in the anteromedial region, including the *supraoptic nucleus* and *paraventricular nuclei*, send axonal projections into the posterior pituitary gland. There they stimulate the gland to release the hormones vasopressin and oxytocin into the blood to regulate water retention in the kidneys, milk production, and uterine contractility, among other functions. Circulating peptide hormones in the bloodstream can also act on distant sites and influence a wide range of behaviors, from the fight-or-flight response to maternal bonding. The hypothalamus can itself be stimulated by hormones circulating in the blood that were produced in other regions of the body.

The Telencephalon: Cerebrum

Toward the front of and evolutionarily newer than the diencephalon, the telencephalon develops into the cerebrum, which includes most of the limbic system's structures, the basal ganglia, the olfactory bulb, and, covering it all, the cerebral cortex, which we will explore in detail