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NEUROSCIENCE

Exploring the Brain

**Fourth
Edition**



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NEUROSCIENCE

EXPLORING THE BRAIN

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NEUROSCIENCE

EXPLORING THE BRAIN

FOURTH EDITION

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Prepress Vendor: Absolute Service, Inc.

Fourth Edition

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9 8 7 6 5 4 3 2 1

Printed in China

Library of Congress Cataloging-in-Publication Data

Bear, Mark F., author.

Neuroscience : exploring the brain / Mark F. Bear, Barry W. Connors, Michael A. Paradiso. — Fourth edition.
p. ; cm.

Includes bibliographical references and index.

ISBN 978-0-7817-7817-6 (hardback : alk. paper)

I. Connors, Barry W., author. II. Paradiso, Michael A., author. III. Title.

[DNLM: 1. Brain. 2. Neurosciences. 3. Spinal Cord. WL 300]

QP355.2

Proudly sourced and uploaded by [StormRG]

612.8—dc23

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DEDICATION

Anne, David, and Daniel
Ashley, Justin, and Kendall

Brian and Jeffrey

Wendy, Bear, and Boo

PREFACE



THE ORIGINS OF *NEUROSCIENCE: EXPLORING THE BRAIN*

For over 30 years, we have taught a course called Neuroscience 1: An Introduction to the Nervous System. “Neuro 1” has been remarkably successful. At Brown University, where the course originated, approximately one out of every four undergraduates takes it. For a few students, this is the beginning of a career in neuroscience; for others, it is the only science course they take in college.

The success of introductory neuroscience reflects the fascination and curiosity everyone has for how we sense, move, feel, and think. However, the success of our course also derives from the way it is taught and what is emphasized. First, there are no prerequisites, so the elements of biology, chemistry, and physics required for understanding neuroscience are covered as the course progresses. This approach ensures that no students are left behind. Second, liberal use of commonsense metaphors, real-world examples, humor, and anecdotes remind students that science is interesting, approachable, exciting, and fun. Third, the course does not survey all of neurobiology. Instead, the focus is on mammalian brains and, whenever possible, the human brain. In this sense, the course closely resembles what is taught to most beginning medical students. Similar courses are now offered at many colleges and universities by psychology, biology, and neuroscience departments.

The first edition of *Neuroscience: Exploring the Brain* was written to provide a suitable textbook for Neuro 1, incorporating the subject matter and philosophy that made this course successful. Based on feedback from our students and colleagues at other universities, we expanded the second edition to include more topics in behavioral neuroscience and some new features to help students understand the structure of the brain. In the third edition, we shortened chapters when possible by emphasizing principles more and details less and made the book even more user-friendly by improving the layout and clarity of the illustrations. We must have gotten it right because the book now ranks as one of the most popular introductory neuroscience books in the world. It has been particularly gratifying to see our book used as a catalyst for the creation of new courses in introductory neuroscience.

NEW IN THE FOURTH EDITION

The advances in neuroscience since publication of the third edition have been nothing short of breathtaking. The elucidation of the human genome has lived up to its promise to “change everything” we know about our brains. We now have insight into how neurons differ at the molecular level, and this knowledge has been exploited to develop revolutionary technologies to trace their connections and interrogate their functions. The genetic basis for many neurological and psychiatric diseases has been revealed. The methods of genetic engineering have made it possible to create animal models to examine how genes and genetically defined circuits contribute to brain function. Skin cells derived from patients have

been transformed into stem cells, and these have been transformed into neurons that reveal how cellular functions go awry in diseases and how the brain might be repaired. New imaging and computational methods now put within reach the dream of creating a “wiring diagram” for the entire brain. A goal for the fourth edition was to make these and other exciting new developments accessible to the first-time neuroscience student.

We authors are all active neuroscientists, and we want our readers to understand the allure of brain research. A unique feature of our book is the *Path of Discovery* boxes, in which famous neuroscientists tell stories about their own research. These essays serve several purposes: to give a flavor of the thrill of discovery; to show the importance of hard work and patience, as well as serendipity and intuition; to reveal the human side of science; and to entertain and amuse. We have continued this tradition in the fourth edition, with contributions from 26 esteemed scientists. Included in this illustrious group are Nobel laureates Mario Capecchi, Eric Kandel, Leon Cooper, May-Britt Moser, and Edvard Moser.

AN OVERVIEW OF THE BOOK

Neuroscience: Exploring the Brain surveys the organization and function of the human nervous system. We present material at the cutting edge of neuroscience in a way that is accessible to both science and nonscience students alike. The level of the material is comparable to an introductory college text in general biology.

The book is divided into four parts: Part I, Foundations; Part II, Sensory and Motor Systems; Part III, The Brain and Behavior; and Part IV, The Changing Brain. We begin Part I by introducing the modern field of neuroscience and tracing some of its historical antecedents. Then we take a close look at the structure and function of individual neurons, how they communicate chemically, and how these building blocks are arranged to form a nervous system. In Part II, we go inside the brain to examine the structure and function of the systems that serve the senses and command voluntary movements. In Part III, we explore the neurobiology of human behavior, including motivation, sex, emotion, sleep, language, attention, and mental illness. Finally, in Part IV, we look at how the environment modifies the brain, both during development and in adult learning and memory.

The human nervous system is examined at several different scales, ranging from the molecules that determine the functional properties of neurons to the large systems in the brain that underlie cognition and behavior. Many disorders of the human nervous system are introduced as the book progresses, usually within the context of the specific neural system under discussion. Indeed, many insights into the normal functions of neural systems have come from the study of diseases that cause specific malfunctions of these systems. In addition, we discuss the actions of drugs and toxins on the brain using this information to illustrate how different brain systems contribute to behavior and how drugs may alter brain function.

Organization of Part I: Foundations (Chapters 1–7)

The goal of Part I is to build a strong base of general knowledge in neurobiology. The chapters should be covered sequentially, although Chapters 1 and 6 can be skipped without a loss of continuity.

In Chapter 1, we use an historical approach to review some basic principles of nervous system function and then turn to the topic of how neuroscience research is conducted today. We directly confront the ethics of neuroscience research, particularly that which involves animals.

In Chapter 2, we focus mainly on the cell biology of the neuron. This is essential information for students inexperienced in biology, and we find that even those with a strong biology background find this review helpful. After touring the cell and its organelles, we go on to discuss the structural features that make neurons and their supporting cells unique, emphasizing the correlation of structure and function. We also introduce some of the feats of genetic engineering that neuroscientists now use routinely to study the functions of different types of nerve cell.

Chapters 3 and 4 are devoted to the physiology of the neuronal membrane. We cover the essential chemical, physical, and molecular properties that enable neurons to conduct electrical signals. We discuss the principles behind the revolutionary new methods of optogenetics. Throughout the chapter, we appeal to students' intuition by using a commonsense approach, with a liberal use of metaphors and real-life analogies.

Chapters 5 and 6 cover interneuronal communication, particularly chemical synaptic transmission. Chapter 5 presents the general principles of chemical synaptic transmission, and Chapter 6 discusses the neurotransmitters and their modes of action in greater detail. We also describe many of the modern methods for studying the chemistry of synaptic transmission. Later chapters do not assume an understanding of synaptic transmission at the depth of Chapter 6, however, so this chapter can be skipped at the instructor's discretion. Most coverage of psychopharmacology appears in Chapter 15, after the general organization of the brain and its sensory and motor systems have been presented. In our experience, students wish to know where, in addition to how, drugs act on the nervous system and behavior.

Chapter 7 covers the gross anatomy of the nervous system. Here we focus on the common organizational plan of the mammalian nervous system by tracing the brain's embryological development. (Cellular aspects of development are covered in Chapter 23.) We show that the specializations of the human brain are simple variations on the basic plan that applies to all mammals. We introduce the cerebral cortex and the new field of connectomics.

Chapter 7's appendix, *An Illustrated Guide to Human Neuroanatomy*, covers the surface and cross-sectional anatomy of the brain, the spinal cord, the autonomic nervous system, the cranial nerves, and the blood supply. A self-quiz will help students learn the terminology. We recommend that students become familiar with the anatomy in the guide before moving on to Part II. The coverage of anatomy is selective, emphasizing the relationship of structures that will be covered in later chapters. We find that students love to learn the anatomy.

Organization of Part II: Sensory and Motor Systems (Chapters 8–14)

Part II surveys the systems within the brain that control sensation and movement. In general, these chapters do not need to be covered sequentially, except for Chapters 9 and 10 on vision and Chapters 13 and 14 on the control of movement.

We chose to begin Part II with a discussion of the chemical senses—smell and taste—in Chapter 8. These are good systems for illustrating the general principles and problems in the encoding of sensory information, and the transduction mechanisms have strong parallels with other systems.

Chapters 9 and 10 cover the visual system, an essential topic for all introductory neuroscience courses. Many details of visual system organization are presented, illustrating not only the depth of current knowledge but also the principles that apply across sensory systems.

Chapter 11 explores the auditory system, and Chapter 12 introduces the somatic sensory system. Audition and somatic sensation are such important parts of everyday life; it is hard to imagine teaching introductory neuroscience without discussing them. The vestibular sense of balance is covered in a separate section of Chapter 11. This placement offers instructors the option to skip the vestibular system at their discretion.

In Chapters 13 and 14, we discuss the motor systems of the brain. Considering how much of the brain is devoted to the control of movement, this more extensive treatment is clearly justified. However, we are well aware that the complexities of the motor systems are daunting to students and instructors alike. We have tried to keep our discussion sharply focused, using numerous examples to connect with personal experience.

Organization of Part III: The Brain and Behavior (Chapters 15–22)

Part III explores how different neural systems contribute to different behaviors, focusing on the systems where the connection between the brain and behavior can be made most strongly. We cover the systems that control visceral function and homeostasis, simple motivated behaviors such as eating and drinking, sex, mood, emotion, sleep, consciousness, language, and attention. Finally, we discuss what happens when these systems fail during mental illness.

Chapters 15–19 describe a number of neural systems that orchestrate widespread responses throughout the brain and the body. In Chapter 15, we focus on three systems that are characterized by their broad influence and their interesting neurotransmitter chemistry: the secretory hypothalamus, the autonomic nervous system, and the diffuse modulatory systems of the brain. We discuss how the behavioral manifestations of various drugs may result from disruptions of these systems.

In Chapter 16, we look at the physiological factors that motivate specific behaviors, focusing mainly on recent research about the control of eating habits. We also discuss the role of dopamine in motivation and addiction, and we introduce the new field of “neuroeconomics.” Chapter 17 investigates the influence of sex on the brain, and the influence of the brain on sexual behavior. Chapter 18 examines the neural systems believed to underlie emotional experience and expression, specifically emphasizing fear and anxiety, anger, and aggression.

In Chapter 19, we investigate the systems that give rise to the rhythms of the brain, ranging from the rapid electrical rhythms during sleep and wakefulness to the slow circadian rhythms controlling hormones, temperature, alertness, and metabolism. We next explore aspects of brain processing that are highly developed in the human brain. Chapter 20 investigates the neural basis of language and Chapter 21 discusses changes in brain activity associated with rest, attention, and consciousness. Part III ends with a discussion of mental illness in Chapter 22. We introduce the promise of molecular medicine to develop new treatments for serious psychiatric disorders.

Organization of Part IV: The Changing Brain (Chapters 23–25)

Part IV explores the cellular and molecular basis of brain development and learning and memory. These subjects represent two of the most exciting frontiers of modern neuroscience.

Chapter 23 examines the mechanisms used during brain development to ensure that the correct connections are made between neurons. The cellular aspects of development are discussed here rather than in Part I

for several reasons. First, by this point in the book, students fully appreciate that normal brain function depends on its precise wiring. Because we use the visual system as a concrete example, the chapter must also follow a discussion of the visual pathways in Part II. Second, we survey aspects of experience-dependent development of the visual system that are regulated by behavioral state, so this chapter is placed after the early chapters of Part III. Finally, an exploration of the role of the sensory environment in brain development in Chapter 23 is followed in the next two chapters by discussions of how experience-dependent modifications of the brain form the basis for learning and memory. We see that many of the mechanisms are similar, illustrating the unity of biology.

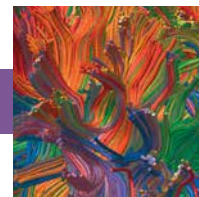
Chapters 24 and 25 cover learning and memory. Chapter 24 focuses on the anatomy of memory, exploring how different parts of the brain contribute to the storage of different types of information. Chapter 25 takes a deeper look into the molecular and cellular mechanisms of learning and memory, focusing on changes in synaptic connections.

HELPING STUDENTS LEARN

Neuroscience: Exploring the Brain is not an exhaustive study. It is intended to be a readable textbook that communicates to students the important principles of neuroscience clearly and effectively. To help students learn neuroscience, we include a number of features designed to enhance comprehension:

- **Chapter Outlines and Introductory and Concluding Remarks.** These elements preview the organization of each chapter, set the stage, and place the material into broader perspective.
- **Of Special Interest Boxes.** These boxes are designed to illuminate the relevance of the material to the students' everyday lives.
- **Brain Food Boxes.** More advanced material that might be optional in many introductory courses is set aside for students who want to go deeper.
- **Path of Discovery Boxes.** These essays, written by leading researchers, demonstrate a broad range of discoveries and the combination of hard work and serendipity that led to them. These boxes both personalize scientific exploration and deepen the reader's understanding of the chapter material and its implications.
- **Key Terms and Glossary.** Neuroscience has a language of its own, and to comprehend it, one must learn the vocabulary. In the text of each chapter, important terms are highlighted in boldface type. To facilitate review, these terms appear in a list at the end of each chapter in the order in which they appeared in the text, along with page references. The same terms are assembled at the end of the book, with definitions, in a glossary.
- **Review Questions.** At the end of each chapter, a brief set of questions for review are specifically designed to provoke thought and help students integrate the material.
- **Further Reading.** We include a list of several recent review articles at the end of each chapter to guide study beyond the scope of the textbook.
- **Internal Reviews of Neuroanatomical Terms.** In Chapter 7, where nervous system anatomy is discussed, the narrative is interrupted periodically with brief self-quiz vocabulary reviews to enhance understanding. In Chapter 7's appendix, an extensive self-quiz is provided in the form of a workbook with labeling exercises.

- **References and Resources.** At the end of the book, we provide selected readings and online resources that will lead students into the research literature associated with each chapter. Rather than including citations in the body of the chapters, where they would compromise the readability of the text, we have organized the references and resources by chapter and listed them at the end of the book.
- **Full-Color Illustrations.** We believe in the power of illustrations—not those that “speak a thousand words” but those that each make a single point. The first edition of this book set a new standard for illustrations in a neuroscience text. The fourth edition reflects improvements in the pedagogical design of many figures from earlier editions and includes many superb new illustrations as well.



Succeed in your course and discover the excitement of the dynamic, rapidly changing field of neuroscience with this fourth edition of *Neuroscience: Exploring the Brain*. This user's guide will help you discover how to best use the features of this book.

Chapter Outline

This "road map" to the content outlines what you will learn in each chapter and can serve as a valuable review tool.

CHAPTER ONE

Neuroscience: Past, Present, and Future

INTRODUCTION

THE ORIGINS OF NEUROSCIENCE

- Views of the Brain in Ancient Greece
- Views of the Brain During the Roman Empire
- Views of the Brain from the Renaissance to the Nineteenth Century
- Nineteenth-Century Views of the Brain
- Nerves as Wires
- Localization of Specific Functions to Different Parts of the Brain
- The Evolution of Nervous Systems
- The Neuron: The Basic Functional Unit of the Brain

NEUROSCIENCE TODAY

Levels of Analysis

- Molecular Neuroscience
- Cellular Neuroscience
- Systems Neuroscience
- Behavioral Neuroscience
- Cognitive Neuroscience

Neuroscientists

The Scientific Process

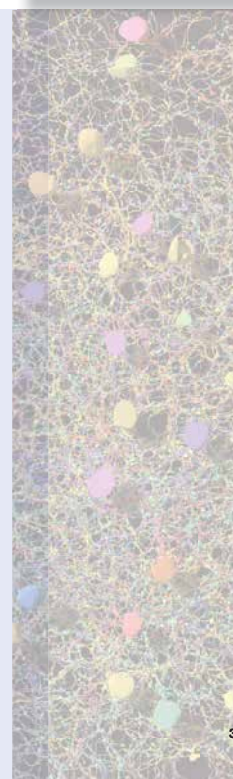
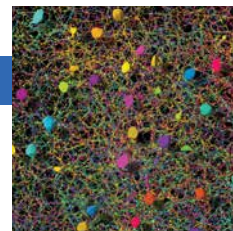
- Observation
- Replication
- Interpretation
- Verification

The Use of Animals in Neuroscience Research

- The Animals
- Animal Welfare
- Animal Rights

The Cost of Ignorance: Nervous System Disorders

CONCLUDING REMARKS



3



BOX 2.2 BRAIN FOOD

Expressing One's Mind in the Post-Genomic Era

Sequencing the human genome was a truly monumental achievement, completed in 2003. The Human Genome Project identified all of the approximately 25,000 genes in human DNA. We now live in what has been called the "post-genomic era," in which information about the genes expressed in our tissues can be used to diagnose and treat diseases. Neuroscientists are using this information to tackle long-standing questions about the biological basis of neurological and psychiatric disorders as well as to probe deeper into the origins of individuality. The logic goes as follows. The brain is a product of the genes expressed in it. Differences in gene expression between a normal brain and a diseased brain, or a brain of unusual ability, can be used to identify the molecular basis of the observed symptoms or traits.

The level of gene expression is usually defined as the number of mRNA transcripts synthesized by different cells and tissues to direct the synthesis of specific proteins. Thus, the analysis of gene expression requires comparing the relative abundance of various mRNAs in the brains of two groups of humans or animals. One way to perform such a comparison is to use DNA microarrays, which are created by robotic machines that arrange thousands of small spots of synthetic DNA on a microscope slide. Each spot contains a unique DNA sequence that will recognize and stick to a different specific mRNA sequence. To compare the gene expression in two brains, one begins by collecting a sample of mRNAs from each brain. The mRNA of one brain is labeled with a chemical tag that fluoresces green, and the mRNA of the other brain is labeled with a tag that fluoresces red. These samples are then applied to the microarray. Highly expressed genes will produce brightly fluorescent spots, and differences in the relative gene expression between the brains will be revealed by differences in the color of the fluorescence (Figure A).

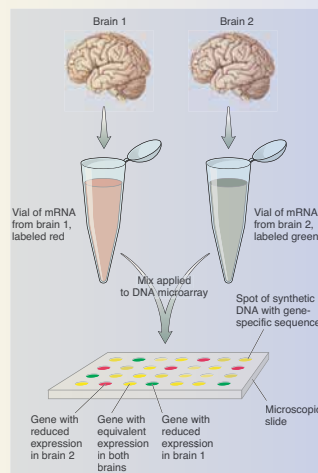


Figure A
Profiling differences in gene expression.

Brain Food Boxes

Want to expand your understanding? These boxes offer optional advanced material so you can expand on what you've learned.



BOX 16.2 OF SPECIAL INTEREST

Marijuana and the Munchies

A well-known consequence of marijuana intoxication is stimulation of appetite, an effect known by users as "the munchies." The active ingredient in marijuana is Δ^9 -tetrahydrocannabinol (THC), which alters neuronal functions by stimulating a receptor called cannabinoid receptor 1 (CB1). CB1 receptors are abundant throughout the brain, so it is overly simplistic to view these receptors as serving only appetite regulation. Nevertheless, "medical marijuana" is often prescribed (where legal) as a means to stimulate appetite in patients with chronic diseases, such as cancer and AIDS. A compound that inhibits CB1 receptors, rimonabant, was also developed as an appetite suppressant. However, human drug trials had to be discontinued because of psychiatric side effects. Although this finding underscores the fact that these receptors do much more than mediate the munchies, it is still of interest to know where in the brain CB1 receptors act to stimulate appetite. Not surprisingly, the CB1 receptors are associated with neurons in many regions of the brain that control feeding, such as the hypothalamus, and some of the orexigenic effects of THC are related to changing the activity of these neurons. However, neuroscientists were surprised to learn in 2014 that much of the appetite stimulation comes from enhancing the sense of smell, at least in

mice. Collaborative research conducted by neuroscientists in France and Spain, countries incidentally known for their appreciation of good tastes and smells, revealed that activation of CB1 receptors in the olfactory bulb increases odor detection and is necessary for the increase in food intake stimulated in hungry mice by cannabinoids.

In Chapter 8, we discussed how smells activate neurons in the olfactory bulb which, in turn, relay information to the olfactory cortex. The cortex also sends feedback projections to the bulb that synapse on inhibitory interneurons called granule cells. By activating the inhibitory granule cells, this feedback from the cortex dampens ascending olfactory activity. These corticofugal synapses use glutamate as a neurotransmitter. The brain's own endocannabinoids (anandamide and 2-arachidonoylglycerol) are synthesized under fasting conditions, and they inhibit glutamate release by acting on CB1 receptors on the corticofugal axon terminals. Reducing granule cell activation by glutamate in the bulb has the net effect of enhancing the sense of smell (Figure A). It remains to be determined if the munchies arise from enhanced olfaction in marijuana users, but a simple experiment, such as holding your nose while eating, confirms that much of the hedonic value of food derives from the sense of smell.

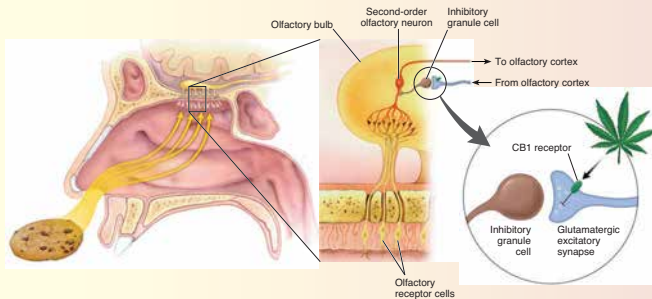


Figure A Activation of CB1 receptors by THC, the psychoactive ingredient in marijuana, enhances olfaction by suppressing the release of glutamate from corticofugal inputs to inhibitory granule cells in the olfactory bulb. (Source: Adapted from Soria-Gomez et al., 2014.)

Of Special Interest Boxes

Wondering how key concepts appear in the real world? These boxes complement the text by showing some of the more practical applications of concepts. Topics include brain disorders, human case studies, drugs, new technology, and more.



BOX 2.3 PATH OF DISCOVERY

Gene Targeting in Mice

by Mario Capecchi



How did I first get the idea to pursue gene targeting in mice? From a simple observation. Mike Wigler, now at Cold Spring Harbor Laboratory, and Richard Axel, at Columbia University, had published a paper in 1979 showing that exposing mammalian cells to a mixture of DNA and calcium phosphate would cause some cells to take up the DNA in functional form and express the encoded genes. This was exciting because they had clearly demonstrated that exogenous, functional DNA could be introduced into mammalian cells. But I wondered why their efficiency was so low. Was it a problem of delivery, insertion of exogenous DNA into the chromosome, or expression of the genes once inserted into the host chromosome? What would happen if purified DNA was directly injected into the nucleus of mammalian cells in culture?

To find out, I converted a colleague's electrophysiology station into a miniature hypodermic needle to directly inject DNA into the nucleus of a living cell using mechanical micromanipulators and light microscopy (Figure A). The procedure worked with amazing efficiency (Capecchi, 1980). With this method, the frequency of successful integration was now one in three cells rather than one in a million cells as formerly. This high efficiency directly led to the development

of transgenic mice through the injection and random integration of exogenous DNA into chromosomes of fertilized mouse eggs, or zygotes. To achieve the high efficiency of expression of the exogenous DNA in the recipient cell, I had to attach small fragments of viral DNA, which we now understand to contain enhancers that are critical in eukaryotic gene expression.

But what fascinated me most was our observation that when many copies of a gene were injected into a cell nucleus, all of these molecules ended up in an ordered head-to-tail arrangement, called a concatamer (Figure B). This was astonishing and could not have occurred as a random event. We went on to unequivocally prove that homologous recombination, the process by which chromosomes share genetic information during cell division, was responsible for the incorporation of the foreign DNA (Folger et al., 1982). These experiments demonstrated that all mammalian somatic cells contain a very efficient machinery for swapping segments of DNA that have similar sequences of nucleotides. Injection of a thousand copies of a gene sequence into the nucleus of a cell resulted in chromosomal insertion of a concatamer containing a thousand copies of that sequence, all oriented in the same direction. This simple observation directly led me to

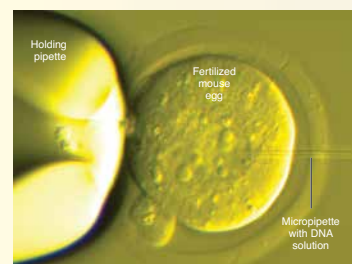


Figure A Fertilized mouse egg receiving an injection of foreign DNA. (Image courtesy of Dr. Peimin Qi, Division of Comparative Medicine, Massachusetts Institute of Technology.)

Path of Discovery Boxes

Learn about some of the superstars in the field with these boxes. Leading researchers describe their discoveries and achievements and tell the story of how they arrived at them.

the anatomical study of brain cells had to await a method to harden the tissue without disturbing its structure and an instrument that could produce very thin slices. Early in the nineteenth century, scientists discovered how to harden, or "fix," tissues by immersing them in formaldehyde, and they developed a special device called a *microtome* to make very thin slices.

These technical advances spawned the field of **histology**, the microscopic study of the structure of tissues. But scientists studying brain structure faced yet another obstacle. Freshly prepared brain tissue has a uniform, cream-colored appearance under the microscope, with no differences in pigmentation to enable histologists to resolve individual cells. The final breakthrough in neurohistology was the introduction of stains that selectively color some, but not all, parts of the cells in brain tissue.

One stain still used today was introduced by the German neurologist Franz Nissl in the late nineteenth century. Nissl showed that a class of basic dyes would stain the nuclei of all cells as well as clumps of material surrounding the nuclei of neurons (Figure 2.1). These clumps are called *Nissl bodies*, and the stain is known as the **Nissl stain**. The Nissl stain is extremely useful for two reasons: It distinguishes between neurons and

The Nucleus. Its name derived from the Latin word for "nut," the **nucleus** of the cell is spherical, centrally located, and about 5–10 μm across. It is contained within a double membrane called the *nuclear envelope*. The nuclear envelope is perforated by pores about 0.1 μm across.

Within the nucleus are **chromosomes** which contain the genetic material **DNA (deoxyribonucleic acid)**. Your DNA was passed on to you from your parents and it contains the blueprint for your entire body. The DNA in each of your neurons is the same, and it is the same as the DNA in the cells of your liver and kidney and other organs. What distinguishes a neuron from a liver cell are the specific parts of the DNA that are used to assemble the cell. These segments of DNA are called **genes**.

Each chromosome contains an uninterrupted double-strand braid of DNA, 2 nm wide. If the DNA from the 46 human chromosomes were laid out straight, end to end, it would measure more than 2 m in length. If we were to compare this total length of DNA to the total string of letters that make up this book, the genes would be analogous to the individual words. Genes are from 0.1 to several micrometers in length.

The "reading" of the DNA is known as **gene expression**. The final product of gene expression is the synthesis of molecules called **proteins**, which exist in a wide variety of shapes and sizes, perform many different functions, and bestow upon neurons virtually all of their unique characteristics. **Protein synthesis**, the assembly of protein molecules, occurs in the cytoplasm. Because the DNA never leaves the nucleus, an intermediary must carry the genetic message to the sites of protein synthesis in the cytoplasm. This function is performed by another long molecule called

arrangement, or **cytoarchitecture** brain. (The prefix *cyto-* is "cytoarchitecture" led to the specialized regions. We now function.



KEY TERMS

Introduction

neuron (p. 24)
glial cell (p. 24)

The Neuron Doctrine

histology (p. 25)
Nissl stain (p. 25)
cytoarchitecture (p. 25)
Golgi stain (p. 26)
cell body (p. 26)
soma (p. 26)
perikaryon (p. 26)
neurite (p. 26)
axon (p. 26)
dendrite (p. 26)
neuron doctrine (p. 27)

The Prototypical Neuron

cytosol (p. 29)
organelle (p. 29)
cytoplasm (p. 29)
nucleus (p. 29)
chromosome (p. 29)
DNA (deoxyribonucleic acid) (p. 29)
gene (p. 29)
gene expression (p. 29)
protein (p. 29)
protein synthesis (p. 29)
mRNA (messenger ribonucleic acid) (p. 29)
transcription (p. 29)
promoter (p. 31)

transcription factor (p. 31)
RNA splicing (p. 31)
amino acid (p. 32)
translation (p. 32)
genome (p. 32)
genetic engineering (p. 32)
knockout mice (p. 33)
transgenic mice (p. 33)
knock-in mice (p. 33)
ribosome (p. 36)
rough endoplasmic reticulum (rough ER) (p. 36)
polyribosome (p. 36)
smooth endoplasmic reticulum (smooth ER) (p. 36)
Golgi apparatus (p. 36)
mitochondrion (p. 36)
ATP (adenosine triphosphate) (p. 38)
neuronal membrane (p. 38)
cytoskeleton (p. 38)
microtubule (p. 38)
microfilament (p. 39)
neurofilament (p. 39)
axon hillock (p. 39)
axon collateral (p. 39)
axon terminal (p. 41)
terminal bouton (p. 41)
synapse (p. 42)
terminal arbor (p. 42)
innervation (p. 42)
synaptic vesicle (p. 42)

synaptic cleft (p. 43)
synaptic transmission (p. 43)
neurotransmitter (p. 43)
axoplasmic transport (p. 43)
anterograde transport (p. 44)
retrograde transport (p. 44)
dendritic tree (p. 44)
receptor (p. 46)
dendritic spine (p. 46)
Classifying Neurons
unipolar neuron (p. 46)
bipolar neuron (p. 46)
multipolar neuron (p. 46)
stellate cell (p. 46)
pyramidal cell (p. 46)
spiny neuron (p. 46)
aspinous neuron (p. 46)
primary sensory neuron (p. 48)
motor neuron (p. 48)
interneuron (p. 48)
green fluorescent protein (GFP) (p. 48)

Glia

astrocyte (p. 49)
oligodendroglial cell (p. 49)
Schwann cell (p. 49)
myelin (p. 49)
node of Ranvier (p. 49)
ependymal cell (p. 52)
microglial cell (p. 52)

Key Terms

Appearing in bold throughout the text, key terms are also listed at the end of each chapter and defined in the glossary. These can help you study and ensure you've mastered the terminology as you progress through your course.



REVIEW QUESTIONS

1. State the neuron doctrine in a single sentence. To whom is this insight credited?
2. Which parts of a neuron are shown by a Golgi stain that are not shown by a Nissl stain?
3. What are three physical characteristics that distinguish axons from dendrites?
4. Of the following structures, state which ones are unique to neurons and which are not: nucleus, mitochondria, rough ER, synaptic vesicle, Golgi apparatus.
5. What are the steps by which the information in the DNA of the nucleus directs the synthesis of a membrane-associated protein molecule?
6. Colchicine is a drug that causes microtubules to break apart (depolymerize). What effect would this drug have on anterograde transport? What would happen in the axon terminal?
7. Classify the cortical pyramidal cell based on (1) the number of neurites, (2) the presence or absence of dendritic spines, (3) connections, and (4) axon length.
8. Knowledge of genes uniquely expressed in a particular category of neurons can be used to understand how those neurons function. Give one example of how you could use genetic information to study a category of neuron.
9. What is myelin? What does it do? Which cells provide it in the central nervous system?

Review Questions

Test your comprehension of each of the chapter's major concepts with these review questions.



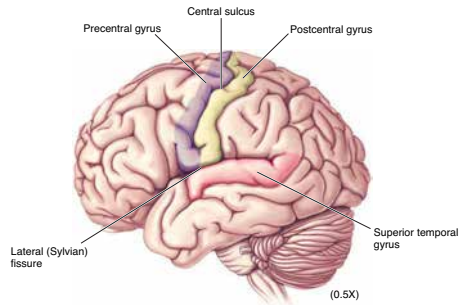
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Further Reading

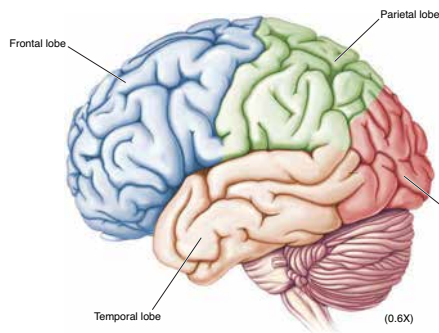
Interested in learning more? Recent review articles are identified at the end of each chapter so you can delve further into the content.

(b) Selected Gyri, Sulci, and Fissures. The cerebrum is noteworthy for its convoluted surface. The bumps are called *gyri*, and the grooves are called *sulci* or, if they are especially deep, *fissures*. The precise pattern of gyri and sulci can vary considerably from individual to individual, but many features are common to all human brains. Some of the important landmarks are labeled here. Notice that



(c) Cerebral Lobes and the Insula. By convention, the cerebrum is subdivided into lobes named after the bones of the skull that lie over them. The central sulcus divides the frontal lobe from the parietal lobe. The temporal lobe lies immediately ventral to the deep lateral (Sylvian) fissure. The occipital lobe lies at the very back

of the cerebrum, bordering both parietal and temporal lobes. A buried piece of the cerebral cortex, called the *insula* (Latin for "island"), is revealed if the margins of the lateral fissure are gently pulled apart (inset). The insula borders and separates the temporal and frontal lobes.



An Illustrated Guide to Human Neuroanatomy

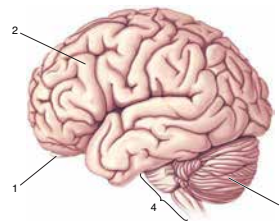
This appendix to Chapter 7 includes an extensive self-quiz with labeling exercises that enable you to assess your knowledge of neuroanatomy.

SELF-QUIZ

This review workbook is designed to help you learn the neuroanatomy that has been presented. Here, we have reproduced the images from the Guide; however, instead of labels, numbered leader lines (arranged in a clockwise fashion) point to the structures of interest. Test your knowledge by filling in the appropriate names in the spaces provided. To review what you have learned, quiz yourself by putting your hand over the names. Experience has shown that this technique greatly facilitates the learning and retention of anatomical terms. Mastery of the vocabulary of neuroanatomy will serve you well as you learn about the functional organization of the brain in the remainder of the book.

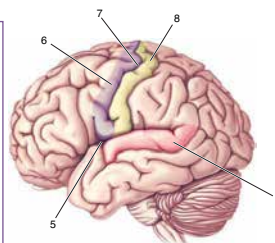
The Lateral Surface of the Brain

(a) Gross Features



1. _____
2. _____
3. _____
4. _____

(b) Selected Gyri, Sulci, and Fissures



5. _____
6. _____
7. _____
8. _____
9. _____

Self-Quiz

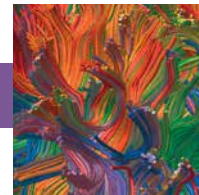
Found in Chapter 7, these brief vocabulary reviews can help enhance your understanding of nervous system anatomy.

SELF-QUIZ

Take a few moments right now and be sure you understand the meaning of these terms:

anterior	ventral	contralateral
rostral	midline	midsagittal plane
posterior	medial	sagittal plane
caudal	lateral	horizontal plane
dorsal	ipsilateral	coronal plane

ACKNOWLEDGMENTS



Back in 1993, when we began in earnest to write the first edition of this textbook, we had the good fortune to work closely with a remarkably dedicated and talented group of individuals—Betsy Dileria, Caitlin and Rob Duckwall, and Suzanne Meagher—who helped us bring the book to fruition. Betsy continued as our developmental editor for the first three editions. We attribute much of our success to her extraordinary efforts to improve the clarity and consistency of the writing and the layout of the book. Betsy's well-deserved retirement caused considerable consternation among the author team, but good fortune struck again with the recruitment of Tom Lochhaas for this new edition. Tom, an accomplished author himself, shares Betsy's attention to detail and challenged us to not rest on our laurels. We are proud of the fourth edition and very grateful to Tom for holding us to a high standard of excellence. We would be remiss for not thanking him also for his good cheer and patience despite a challenging schedule and occasionally distracted authors.

It is noteworthy that despite the passage of time—*21 years!*—we were able to continue working with Caitlin, Rob, and Suzanne in this edition. Caitlin's and Rob's Dragonfly Media Group produced the art, with help and coordination from Jennifer Clements, and the results speak for themselves. The artists took our sometimes fuzzy concepts and made them a beautiful reality. The quality of the art has always been a high priority for the authors, and we are very pleased that they have again delivered an art program that ensures we will continue to enjoy the distinction of having produced the most richly illustrated neuroscience textbook in the world. Finally, we are forever indebted to Suzanne, who assisted us at every step. Without her incredible assistance, loyalty, and dedication to this project, the book would never have been completed. That statement is as true today as it was in 1993. Suzanne, you are—still—the best!

For the current edition, we have the pleasure of acknowledging a new team member, Linda Francis. Linda is an editorial project manager at Lippincott Williams & Wilkins, and she worked closely with us from start to finish, helping us to meet a demanding schedule. Her efficiency, flexibility, and good humor are all greatly appreciated. Linda, it has been a pleasure working with you.

In the publishing industry, editors seem to come and go with alarming frequency. Yet one senior editor at Lippincott Williams & Wilkins stayed the course and continued to be an unwavering advocate for our project: Emily Lupash. We thank you Emily and the entire staff under your direction for your patience and determination to get this edition published.

We again would like to acknowledge the architects and current trustees of the undergraduate neuroscience curriculum at Brown University. We thank Mitchell Glickstein, Ford Ebner, James McIlwain, Leon Cooper, James Anderson, Leslie Smith, John Donoghue, Bob Patrick, and John Stein for all they did to make undergraduate neuroscience great at Brown. Similarly, we thank Sebastian Seung and Monica Linden for their innovative contributions to introductory neuroscience at the Massachusetts Institute of Technology. Monica, who is now on the faculty

of Brown's Department of Neuroscience, also made numerous suggestions for improvements in the fourth edition of this book for which we are particularly grateful.

We gratefully acknowledge the research support provided to us over the years by the National Institutes of Health, the Whitehall Foundation, the Alfred P. Sloan Foundation, the Klingenstein Foundation, the Charles A. Dana Foundation, the National Science Foundation, the Keck Foundation, the Human Frontiers Science Program, the Office of Naval Research, DARPA, the Simons Foundation, the JPB Foundation, the Picower Institute for Learning and Memory, the Brown Institute for Brain Science, and the Howard Hughes Medical Institute.

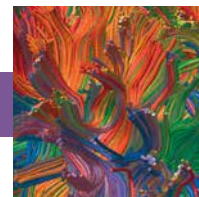
We thank our colleagues in the Brown University Department of Neuroscience and in the Department of Brain and Cognitive Sciences at MIT for their ongoing support of this project and helpful advice. We thank the anonymous but very helpful colleagues at other institutions who gave us comments on the earlier editions. We gratefully acknowledge the scientists who provided us with figures illustrating their research results and, in particular, Satrajit Ghosh and John Gabrieli of MIT for providing the striking image that appears on the cover of the new edition (to learn about the image, see p. xxi). In addition, many students and colleagues helped us to improve the new edition by informing us about recent research, pointing out errors in earlier editions, and suggesting better ways to describe or illustrate concepts. Special thanks to Peter Kind of the University of Edinburgh and Weifeng Xu of MIT.

We are very grateful to our many colleagues who contributed "Path of Discovery" stories. You inspire us.

We thank our loved ones, not only for standing by us as countless weekends and evenings were spent preparing this book, but also for their encouragement and helpful suggestions for improving it.

Finally, we wish to thank the thousands of students we have had the privilege to teach neuroscience over the past 35 years.

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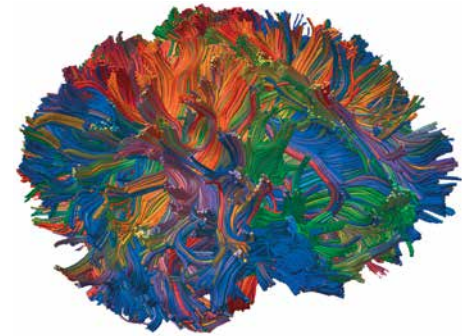
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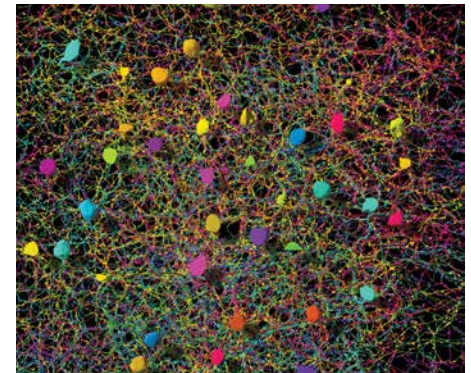
Cortical Barrels



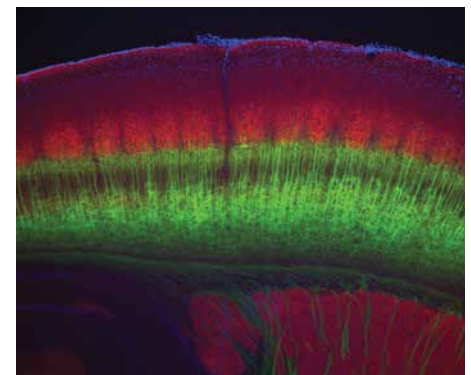
Cover: An image of a living human brain acquired by magnetic resonance tomography to reveal the diffusion of water molecules. Water diffusion in the brain occurs preferentially along bundles of axons. Axons are the “wires” of the nervous system and conduct electrical impulses generated by brain cells. Thus, this image reveals some of the paths of long-range communication between different parts of the brain. The image, acquired at the Athinoula A. Martinos Center for Biomedical Imaging at the Massachusetts Institute of Technology, was processed by a computer algorithm to display bundles of axons traveling together as pseudo-colored noodles. The colors vary depending on the direction of water diffusion. (Source: Courtesy of Satrajit Ghosh and John Gabrieli, McGovern Institute for Brain Research and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology.)

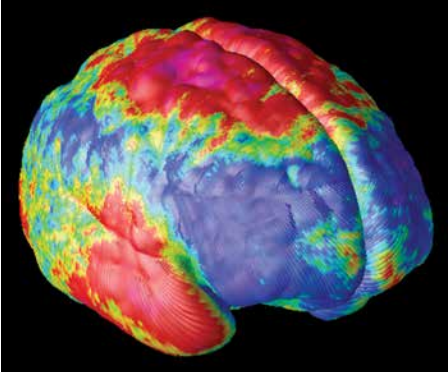


Part One Chapter Opener: Neurons and their neurites. Serial images were taken using an electron microscope of a small piece of the retina as thin slices were shaved off. Then, a computer algorithm, aided by thousands of people worldwide playing an online game called EyeWire, reconstructed each neuron and their synaptic connections—the “connectome” of this volume of tissue. In this image, the neurons are pseudo-colored by the computer, and their neurites, the axons and dendrites from each cell, are displayed in their entirety. (Source: Courtesy of Sebastian Seung, Princeton University, and Kris Krug, Pop Tech.)

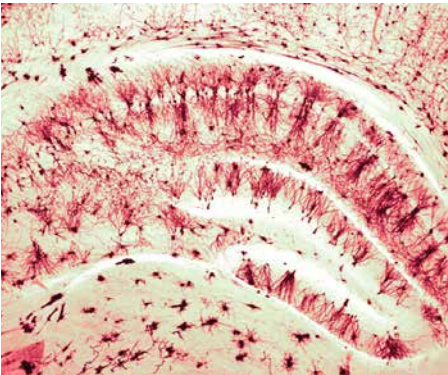


Part Two Chapter Opener: The mouse cerebral cortex. The cerebral cortex lies just under the skull. It is critical for conscious sensory perception and voluntary control of movement. The major subcortical input to the cortex arises from the thalamus, a structure that lies deep inside the brain. Stained red are thalamic axons that bring to the cortex information about the whiskers on the animal’s snout. These are clustered into “barrels” that each represent a single whisker. The neurons that project axons back to the thalamus have been genetically engineered to fluoresce green. Blue indicates the nuclei of other cells stained with a DNA marker. (Source: Courtesy of Shane Crandall, Sandra Patrick, and Barry Connors, Department of Neuroscience, Brown University.)





Part Three Chapter Opener: Gray matter loss in the cerebral cortex of adolescents with schizophrenia. Schizophrenia is a severe mental illness characterized by a loss of contact with reality and a disruption of thought, perception, mood, and movement. The disorder typically becomes apparent during adolescence or early adulthood and persists for life. Symptoms may arise in part from shrinkage of specific parts of the brain, including the cerebral cortex. High-resolution magnetic resonance imaging of the brains of adolescents with schizophrenia has been used to track the location and progression of tissue loss. In this image, the regions of gray matter loss are color coded. Severe tissue loss, up to 5% annually, is indicated in red and pink. Regions colored blue are relatively stable over time. (Source: Courtesy of Arthur Toga and Paul Thompson, Keck School of Medicine, University of Southern California.)



Part Four Chapter Opener: Neurons of the hippocampus. The hippocampus is a brain structure that is critical for our ability to form memories. One way that information is stored in the brain is by modification of synapses, the specialized junctions between the axons of one neuron and the dendrites of another. Synaptic plasticity in the hippocampus has been studied to reveal the molecular basis of memory formation. This image shows the neurites of a subset of hippocampal neurons using a time honored method introduced in 1873 by Italian scientist Emilio Golgi. (Source: Courtesy of Miquel Bosch and Mark Bear, The Picower Institute for Learning and Memory and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology.)



Preface vii
User's Guide xiii
Acknowledgments xvii
Path of Discovery Authors xix
Images xxi

PART ONE Foundations 1

CHAPTER ONE Neuroscience: Past, Present, and Future 3
CHAPTER TWO Neurons and Glia 23
CHAPTER THREE The Neuronal Membrane at Rest 55
CHAPTER FOUR The Action Potential 81
CHAPTER FIVE Synaptic Transmission 109
CHAPTER SIX Neurotransmitter Systems 143
CHAPTER SEVEN The Structure of the Nervous System 179
Appendix: An Illustrated Guide to Human Neuroanatomy 219

PART TWO Sensory and Motor Systems 263

CHAPTER EIGHT The Chemical Senses 265
CHAPTER NINE The Eye 293
CHAPTER TEN The Central Visual System 331
CHAPTER ELEVEN The Auditory and Vestibular Systems 369
CHAPTER TWELVE The Somatic Sensory System 415
CHAPTER THIRTEEN Spinal Control of Movement 453
CHAPTER FOURTEEN Brain Control of Movement 483

PART THREE The Brain and Behavior 519

CHAPTER FIFTEEN Chemical Control of the Brain and Behavior 521
CHAPTER SIXTEEN Motivation 551
CHAPTER SEVENTEEN Sex and the Brain 579
CHAPTER EIGHTEEN Brain Mechanisms of Emotion 615
CHAPTER NINETEEN Brain Rhythms and Sleep 645
CHAPTER TWENTY Language 685
CHAPTER TWENTY-ONE The Resting Brain, Attention, and Consciousness 719
CHAPTER TWENTY-TWO Mental Illness 751

PART FOUR The Changing Brain 781

CHAPTER TWENTY-THREE Wiring the Brain 783
CHAPTER TWENTY-FOUR Memory Systems 823
CHAPTER TWENTY-FIVE Molecular Mechanisms of Learning and Memory 865

Glossary 901
References and Resources 925
Index 953



Preface vii
User's Guide xiii
Acknowledgments xvii
Path of Discovery Authors xix
Images xxi

PART ONE Foundations 1

CHAPTER ONE Neuroscience: Past, Present, and Future 3

INTRODUCTION 4

THE ORIGINS OF NEUROSCIENCE 4

Views of the Brain in Ancient Greece 5
Views of the Brain During the Roman Empire 5
Views of the Brain from the Renaissance to the Nineteenth Century 6
Nineteenth-Century Views of the Brain 8
Nerves as Wires 9
Localization of Specific Functions to Different Parts of the Brain 10
The Evolution of Nervous Systems 11
The Neuron: The Basic Functional Unit of the Brain 12

NEUROSCIENCE TODAY 13

Levels of Analysis 13

Molecular Neuroscience 13
Cellular Neuroscience 13
Systems Neuroscience 13
Behavioral Neuroscience 13
Cognitive Neuroscience 14

Neuroscientists 14

The Scientific Process 15

Observation 15
Replication 15
Interpretation 15
Verification 16

The Use of Animals in Neuroscience Research 16

The Animals 16
Animal Welfare 17
Animal Rights 17

The Cost of Ignorance: Nervous System Disorders 19

CONCLUDING REMARKS 20

CHAPTER TWO Neurons and Glia 23

INTRODUCTION 24

THE NEURON DOCTRINE 24

The Golgi Stain 25
Cajal's Contribution 27

BOX 2.1 OF SPECIAL INTEREST: Advances in Microscopy 28

THE PROTOTYPICAL NEURON 29

The Soma 29

The Nucleus 29
Neuronal Genes, Genetic Variation, and Genetic Engineering 32

BOX 2.2 BRAIN FOOD: Expressing One's Mind in the Post-Genomic Era 33

BOX 2.3 PATH OF DISCOVERY: Gene Targeting in Mice, by Mario Capecchi 34

Rough Endoplasmic Reticulum 36
Smooth Endoplasmic Reticulum and the Golgi Apparatus 36
The Mitochondrion 36

The Neuronal Membrane 38

The Cytoskeleton 38*Microtubules 38***BOX 2.4 OF SPECIAL INTEREST:** Alzheimer's Disease and the Neuronal Cytoskeleton 40*Microfilaments 39**Neurofilaments 39***The Axon 39***The Axon Terminal 41**The Synapse 43**Axoplasmic Transport 43***BOX 2.5 OF SPECIAL INTEREST:** Hitching a Ride with Retrograde Transport 45**Dendrites 44****BOX 2.6 OF SPECIAL INTEREST:** Intellectual Disability and Dendritic Spines 47**CLASSIFYING NEURONS 46****Classification Based on Neuronal Structure 46***Number of Neurites 46**Dendrites 46**Connections 48**Axon Length 48***Classification Based on Gene Expression 48****BOX 2.7 BRAIN FOOD:** Understanding Neuronal Structure and Function with Incredible Cre 50**GLIA 49***Astrocytes 49**Myelinating Glia 49**Other Non-Neuronal Cells 52***CONCLUDING REMARKS 53****CHAPTER THREE The Neuronal Membrane at Rest 55****INTRODUCTION 56****THE CAST OF CHEMICALS 57****Cytosol and Extracellular Fluid 57***Water 58**Ions 58***The Phospholipid Membrane 59****Protein 59***Protein Structure 59**Channel Proteins 62**Ion Pumps 63***THE MOVEMENT OF IONS 64****Diffusion 64****BOX 3.1 BRAIN FOOD:** A Review of Moles and Molarity 65**Electricity 64****THE IONIC BASIS OF THE RESTING MEMBRANE POTENTIAL 66****Equilibrium Potentials 67****BOX 3.2 BRAIN FOOD:** The Nernst Equation 70**The Distribution of Ions Across the Membrane 70****Relative Ion Permeabilities of the Membrane at Rest 72****BOX 3.3 BRAIN FOOD:** The Goldman Equation 73*The Wide World of Potassium Channels 73***BOX 3.4 PATH OF DISCOVERY:** Feeling Around Inside Ion Channels in the Dark, by Chris Miller 76*The Importance of Regulating the External Potassium Concentration 75***BOX 3.5 OF SPECIAL INTEREST:** Death by Lethal Injection 78**CONCLUDING REMARKS 78****CHAPTER FOUR The Action Potential 81****INTRODUCTION 82****PROPERTIES OF THE ACTION POTENTIAL 82****The Ups and Downs of an Action Potential 82****BOX 4.1 BRAIN FOOD:** Methods of Recording Action Potentials 83

The Generation of an Action Potential	82
The Generation of Multiple Action Potentials	84
<i>Optogenetics: Controlling Neural Activity with Light</i>	86
BOX 4.2 PATH OF DISCOVERY: The Discovery of the Channelrhodopsins, by Georg Nagel	86
THE ACTION POTENTIAL, IN THEORY	88
Membrane Currents and Conductances	88
The Ins and Outs of an Action Potential	90
THE ACTION POTENTIAL, IN REALITY	90
The Voltage-Gated Sodium Channel	92
<i>Sodium Channel Structure</i>	92
<i>Functional Properties of the Sodium Channel</i>	94
BOX 4.3 BRAIN FOOD: The Patch-Clamp Method	95
<i>The Effects of Toxins on the Sodium Channel</i>	96
Voltage-Gated Potassium Channels	97
Putting the Pieces Together	98
ACTION POTENTIAL CONDUCTION	100
Factors Influencing Conduction Velocity	101
BOX 4.4 OF SPECIAL INTEREST: Local Anesthesia	102
Myelin and Saltatory Conduction	103
BOX 4.5 OF SPECIAL INTEREST: Multiple Sclerosis, a Demyelinating Disease	103
ACTION POTENTIALS, AXONS, AND DENDRITES	104
BOX 4.6 OF SPECIAL INTEREST: The Eclectic Electric Behavior of Neurons	106
CONCLUDING REMARKS	107
CHAPTER FIVE Synaptic Transmission	109
INTRODUCTION	110
BOX 5.1 OF SPECIAL INTEREST: Otto Loewi's Dream	111
TYPES OF SYNAPSES	111
Electrical Synapses	111
Chemical Synapses	113
<i>CNS Chemical Synapses</i>	115
BOX 5.2 PATH OF DISCOVERY: For the Love of Dendritic Spines, by Kristen M. Harris	118
<i>The Neuromuscular Junction</i>	119
PRINCIPLES OF CHEMICAL SYNAPTIC TRANSMISSION	119
Neurotransmitters	119
Neurotransmitter Synthesis and Storage	122
Neurotransmitter Release	122
BOX 5.3 BRAIN FOOD: How to SNARE a Vesicle	125
Neurotransmitter Receptors and Effectors	124
<i>Transmitter-Gated Ion Channels</i>	124
BOX 5.4 BRAIN FOOD: Reversal Potentials	127
<i>G-Protein-Coupled Receptors</i>	126
<i>Autoreceptors</i>	128
Neurotransmitter Recovery and Degradation	130
Neuropharmacology	130
BOX 5.5 OF SPECIAL INTEREST: Bacteria, Spiders, Snakes, and People	131
PRINCIPLES OF SYNAPTIC INTEGRATION	132
The Integration of EPSPs	132
<i>Quantal Analysis of EPSPs</i>	132
<i>EPSP Summation</i>	133
The Contribution of Dendritic Properties to Synaptic Integration	133
<i>Dendritic Cable Properties</i>	133
<i>Excitable Dendrites</i>	136
Inhibition	136
BOX 5.6 OF SPECIAL INTEREST: Startling Mutations and Poisons	137
<i>IPSPs and Shunting Inhibition</i>	136
<i>The Geometry of Excitatory and Inhibitory Synapses</i>	138
Modulation	138
CONCLUDING REMARKS	140

CHAPTER SIX Neurotransmitter Systems 143**INTRODUCTION 144****STUDYING NEUROTRANSMITTER SYSTEMS 145****Localization of Transmitters and Transmitter-Synthesizing Enzymes 145***Immunocytochemistry 145**In Situ Hybridization 146***Studying Transmitter Release 148****Studying Synaptic Mimicry 148****Studying Receptors 149***Neuropharmacological Analysis 149**Ligand-Binding Methods 151***BOX 6.1 PATH OF DISCOVERY: Finding Opiate Receptors, by Solomon H. Snyder 152***Molecular Analysis 152***NEUROTRANSMITTER CHEMISTRY 153****Cholinergic Neurons 154****BOX 6.2 BRAIN FOOD: Pumping Ions and Transmitters 154****Catecholaminergic Neurons 156****Serotonergic Neurons 158****Amino Acidergic Neurons 159****Other Neurotransmitter Candidates and Intercellular Messengers 160****BOX 6.3 OF SPECIAL INTEREST: This Is Your Brain on Endocannabinoids 161****TRANSMITTER-GATED CHANNELS 163****The Basic Structure of Transmitter-Gated Channels 163****Amino Acid-Gated Channels 164***Glutamate-Gated Channels 165***BOX 6.4 OF SPECIAL INTEREST: Exciting Poisons: Too Much of a Good Thing 167***GABA-Gated and Glycine-Gated Channels 167***G-PROTEIN-COUPLED RECEPTORS AND EFFECTORS 169****The Basic Structure of G-Protein-Coupled Receptors 169****The Ubiquitous G-Proteins 170****G-Protein-Coupled Effector Systems 170***The Shortcut Pathway 171**Second Messenger Cascades 172**Phosphorylation and Dephosphorylation 174**The Function of Signal Cascades 174***DIVERGENCE AND CONVERGENCE IN NEUROTRANSMITTER SYSTEMS 176****CONCLUDING REMARKS 177****CHAPTER SEVEN The Structure of the Nervous System 179****INTRODUCTION 180****GROSS ORGANIZATION OF THE MAMMALIAN NERVOUS SYSTEM 180****Anatomical References 180****The Central Nervous System 183***The Cerebrum 183**The Cerebellum 183**The Brain Stem 183**The Spinal Cord 183***The Peripheral Nervous System 184***The Somatic PNS 184**The Visceral PNS 185**Afferent and Efferent Axons 185***The Cranial Nerves 185****The Meninges 185****The Ventricular System 186****BOX 7.1 OF SPECIAL INTEREST: Water on the Brain 187****New Views of the Brain 186***Imaging the Structure of the Living Brain 188***BOX 7.2 BRAIN FOOD: Magnetic Resonance Imaging 189***Functional Brain Imaging 188***BOX 7.3 BRAIN FOOD: PET and fMRI 190**

UNDERSTANDING CNS STRUCTURE THROUGH DEVELOPMENT 192**Formation of the Neural Tube 193****BOX 7.4 OF SPECIAL INTEREST:** Nutrition and the Neural Tube 194**Three Primary Brain Vesicles 195****Differentiation of the Forebrain 196***Differentiation of the Telencephalon and Diencephalon 196**Forebrain Structure-Function Relationships 198***Differentiation of the Midbrain 199***Midbrain Structure-Function Relationships 200***Differentiation of the Hindbrain 200***Hindbrain Structure-Function Relationships 202***Differentiation of the Spinal Cord 203***Spinal Cord Structure-Function Relationships 203***Putting the Pieces Together 204****Special Features of the Human CNS 205****A GUIDE TO THE CEREBRAL CORTEX 208****Types of Cerebral Cortex 208****Areas of Neocortex 210***Neocortical Evolution and Structure-Function Relationships 211***BOX 7.5 PATH OF DISCOVERY:** Connecting with the Connectome,
by Sebastian Seung 212**CONCLUDING REMARKS 214****APPENDIX: AN ILLUSTRATED GUIDE TO HUMAN NEUROANATOMY 219****PART TWO Sensory and Motor Systems 263****CHAPTER EIGHT The Chemical Senses 265****INTRODUCTION 266****TASTE 266****The Basic Tastes 267****The Organs of Taste 267****BOX 8.1 OF SPECIAL INTEREST:** Strange Tastes: Fat, Starch, Carbonation,
Calcium, Water? 268**Taste Receptor Cells 269****Mechanisms of Taste Transduction 271***Saltiness 271**Sourness 272**Bitterness 273**Sweetness 273**Umami (Amino Acids) 274***Central Taste Pathways 274****BOX 8.2 OF SPECIAL INTEREST:** Memories of a Very Bad Meal 276**The Neural Coding of Taste 277****SMELL 278****The Organs of Smell 278****BOX 8.3 OF SPECIAL INTEREST:** Human Pheromones? 279**Olfactory Receptor Neurons 280***Olfactory Transduction 280**Olfactory Receptor Proteins 282**cAMP-Gated Channels 283***BOX 8.4 PATH OF DISCOVERY:** Channels of Vision and Smell,
by Geoffrey Gold 284**Central Olfactory Pathways 284****Spatial and Temporal Representations of Olfactory Information 287***Olfactory Population Coding 287**Olfactory Maps 288**Temporal Coding in the Olfactory System 290***CONCLUDING REMARKS 291**

CHAPTER NINE The Eye 293**INTRODUCTION 294****PROPERTIES OF LIGHT 295**

Light 295

Optics 295

THE STRUCTURE OF THE EYE 296

Gross Anatomy of the Eye 296

Ophthalmoscopic Appearance of the Eye 297

BOX 9.1 OF SPECIAL INTEREST: Demonstrating the Blind Regions of Your Eye 298

Cross-Sectional Anatomy of the Eye 298

BOX 9.2 OF SPECIAL INTEREST: Eye Disorders 300**IMAGE FORMATION BY THE EYE 299**

Refraction by the Cornea 299

Accommodation by the Lens 301

BOX 9.3 OF SPECIAL INTEREST: Vision Correction 302

The Pupillary Light Reflex 303

The Visual Field 304

Visual Acuity 304

MICROSCOPIC ANATOMY OF THE RETINA 304

The Laminar Organization of the Retina 305

Photoreceptor Structure 306

BOX 9.4 PATH OF DISCOVERY: Seeing Through the Photoreceptor Mosaic,
by David Williams 308

Regional Differences in Retinal Structure and Their Visual Consequences 310

PHOTOTRANSDUCTION 312

Phototransduction in Rods 312

Phototransduction in Cones 315

Color Perception 316

BOX 9.5 OF SPECIAL INTEREST: The Genetics of Color Vision 317

Dark and Light Adaptation 316

Calcium's Role in Light Adaptation 318

Local Adaptation of Dark, Light, and Color 318

RETINAL PROCESSING AND OUTPUT 319

The Receptive Field 320

Bipolar Cell Receptive Fields 321

Ganglion Cell Receptive Fields 323

Structure-Function Relationships 325

Color-Opponent Ganglion Cells 325

Ganglion Cell Photoreceptors 327

Parallel Processing 328

CONCLUDING REMARKS 328**CHAPTER TEN The Central Visual System 331****INTRODUCTION 332****THE RETINOFUGAL PROJECTION 333**

The Optic Nerve, Optic Chiasm, and Optic Tract 333

Right and Left Visual Hemifields 334

Targets of the Optic Tract 335

BOX 10.1 OF SPECIAL INTEREST: David and Goliath 337

Nonthalamic Targets of the Optic Tract 337

THE LATERAL GENICULATE NUCLEUS 338

The Segregation of Input by Eye and by Ganglion Cell Type 339

Receptive Fields 340

Nonretinal Inputs to the LGN 341

ANATOMY OF THE STRIATE CORTEX 341

Retinotopy 342

Lamination of the Striate Cortex 343

The Cells of Different Layers 344

Inputs and Outputs of the Striate Cortex 344

Innervation of Other Cortical Layers from Layer IVC 345

Ocular Dominance Columns 345

Striate Cortex Outputs 347

Cytochrome Oxidase Blobs 347

PHYSIOLOGY OF THE STRIATE CORTEX 347

Receptive Fields 348

Binocularity 348

Orientation Selectivity 348

BOX 10.2 BRAIN FOOD: Cortical Organization Revealed by Optical and Calcium Imaging 350

Direction Selectivity 350

Simple and Complex Receptive Fields 351

Blob Receptive Fields 353

Parallel Pathways and Cortical Modules 354

Parallel Pathways 354

Cortical Modules 355

BEYOND THE STRIATE CORTEX 356

The Dorsal Stream 358

Area MT 358

Dorsal Areas and Motion Processing 358

The Ventral Stream 359

Area V4 359

Area IT 360

BOX 10.3 PATH OF DISCOVERY: Finding Faces in the Brain, by Nancy Kanwisher 360

FROM SINGLE NEURONS TO PERCEPTION 362

BOX 10.4 OF SPECIAL INTEREST: The Magic of Seeing in 3D 364

Receptive Field Hierarchy and Perception 363

Parallel Processing and Perception 365

CONCLUDING REMARKS 366

CHAPTER ELEVEN The Auditory and Vestibular Systems 369

INTRODUCTION 370

THE NATURE OF SOUND 370

BOX 11.1 OF SPECIAL INTEREST: Ultrasound and Infrasound 372

THE STRUCTURE OF THE AUDITORY SYSTEM 373

THE MIDDLE EAR 374

Components of the Middle Ear 374

Sound Force Amplification by the Ossicles 374

The Attenuation Reflex 376

THE INNER EAR 377

Anatomy of the Cochlea 377

Physiology of the Cochlea 378

The Response of the Basilar Membrane to Sound 379

The Organ of Corti and Associated Structures 380

BOX 11.2 OF SPECIAL INTEREST: The Deaf Shall Hear: Cochlear Implants 382

Transduction by Hair Cells 382

Hair Cells and the Axons of the Auditory Nerve 386

Amplification by Outer Hair Cells 386

BOX 11.3 OF SPECIAL INTEREST: Hearing with Noisy Ears 387

CENTRAL AUDITORY PROCESSES 388

The Anatomy of Auditory Pathways 389

Response Properties of Neurons in the Auditory Pathway 389

ENCODING SOUND INTENSITY AND FREQUENCY 391

Stimulus Intensity 391

Stimulus Frequency, Tonotopy, and Phase Locking 391

Tonotopy 391

Phase Locking 392

BOX 11.4 PATH OF DISCOVERY: Capturing the Beat, by Donata Oertel 394

MECHANISMS OF SOUND LOCALIZATION 395

Localization of Sound in the Horizontal Plane 395

The Sensitivity of Binaural Neurons to Sound Location 396

Localization of Sound in the Vertical Plane 398

AUDITORY CORTEX 399

Neuronal Response Properties 400

BOX 11.5 OF SPECIAL INTEREST: How Does Auditory Cortex Work?
Ask a Specialist 400

The Effects of Auditory Cortical Lesions and Ablation 402

BOX 11.6 OF SPECIAL INTEREST: Auditory Disorders and Their Treatments 402**THE VESTIBULAR SYSTEM 403**

The Vestibular Labyrinth 403

The Otolith Organs 404

The Semicircular Canals 406

Central Vestibular Pathways and Vestibular Reflexes 408

The Vestibulo-Ocular Reflex (VOR) 409

Vestibular Pathology 410

CONCLUDING REMARKS 411**CHAPTER TWELVE The Somatic Sensory System 415****INTRODUCTION 416****TOUCH 416**

Mechanoreceptors of the Skin 417

Vibration and the Pacinian Corpuscle 419*Mechanosensitive Ion Channels* 420*Two-Point Discrimination* 420

Primary Afferent Axons 422

The Spinal Cord 423

Segmental Organization of the Spinal Cord 423**BOX 12.1 OF SPECIAL INTEREST:** Herpes, Shingles, and Dermatomes 426*Sensory Organization of the Spinal Cord* 426

The Dorsal Column–Medial Lemniscal Pathway 426

The Trigeminal Touch Pathway 428

BOX 12.2 BRAIN FOOD: Lateral Inhibition 429

Somatosensory Cortex 430

Cortical Somatotopy 431**BOX 12.3 PATH OF DISCOVERY:** Cortical Barrels, by Thomas Woolsey 434*Cortical Map Plasticity* 435*The Posterior Parietal Cortex* 436**PAIN 437****BOX 12.4 OF SPECIAL INTEREST:** The Misery of Life Without Pain 438

Nociceptors and the Transduction of Painful Stimuli 438

Types of Nociceptors 439*Hyperalgesia and Inflammation* 439**BOX 12.5 OF SPECIAL INTEREST:** Hot and Spicy 440

Itch 441

Primary Afferents and Spinal Mechanisms 442

Ascending Pain Pathways 443

The Spinothalamic Pain Pathway 444*The Trigeminal Pain Pathway* 445*The Thalamus and Cortex* 45

The Regulation of Pain 446

Afferent Regulation 446*Descending Regulation* 446*The Endogenous Opioids* 448**BOX 12.6 OF SPECIAL INTEREST:** Pain and the Placebo Effect 448**TEMPERATURE 449**

Thermoreceptors 449

The Temperature Pathway 451

CONCLUDING REMARKS 451**CHAPTER THIRTEEN Spinal Control of Movement 453****INTRODUCTION 454****THE SOMATIC MOTOR SYSTEM 454****THE LOWER MOTOR NEURON 456**

The Segmental Organization of Lower Motor Neurons 457

Alpha Motor Neurons	458
<i>Graded Control of Muscle Contraction by Alpha Motor Neurons</i>	459
<i>Inputs to Alpha Motor Neurons</i>	459
Types of Motor Units	461
<i>Neuromuscular Matchmaking</i>	461
BOX 13.1 OF SPECIAL INTEREST: ALS: Glutamate, Genes, and Gehrig	463
EXCITATION-CONTRACTION COUPLING	464
BOX 13.2 OF SPECIAL INTEREST: Myasthenia Gravis	464
Muscle Fiber Structure	464
The Molecular Basis of Muscle Contraction	466
BOX 13.3 OF SPECIAL INTEREST: Duchenne Muscular Dystrophy	468
SPINAL CONTROL OF MOTOR UNITS	469
Proprioception from Muscle Spindles	469
<i>The Stretch Reflex</i>	470
BOX 13.4 PATH OF DISCOVERY: Nerve Regeneration Does Not Ensure Full Recovery, by Timothy C. Cope	472
Gamma Motor Neurons	472
Proprioception from Golgi Tendon Organs	475
<i>Proprioception from the Joints</i>	476
Spinal Interneurons	476
<i>Inhibitory Input</i>	477
<i>Excitatory Input</i>	477
The Generation of Spinal Motor Programs for Walking	478
CONCLUDING REMARKS	481
CHAPTER FOURTEEN Brain Control of Movement	483
INTRODUCTION	484
DESCENDING SPINAL TRACTS	485
The Lateral Pathways	486
<i>The Effects of Lateral Pathway Lesions</i>	487
BOX 14.1 OF SPECIAL INTEREST: Paresis, Paralysis, Spasticity, and Babinski	488
The Ventromedial Pathways	488
<i>The Vestibulospinal Tracts</i>	489
<i>The Tectospinal Tract</i>	489
<i>The Pontine and Medullary Reticulospinal Tracts</i>	490
THE PLANNING OF MOVEMENT BY THE CEREBRAL CORTEX	491
Motor Cortex	492
The Contributions of Posterior Parietal and Prefrontal Cortex	493
Neuronal Correlates of Motor Planning	494
BOX 14.2 OF SPECIAL INTEREST: Behavioral Neurophysiology	495
Mirror Neurons	495
THE BASAL GANGLIA	498
Anatomy of the Basal Ganglia	498
Direct and Indirect Pathways through the Basal Ganglia	498
<i>Basal Ganglia Disorders</i>	501
BOX 14.3 OF SPECIAL INTEREST: Do Neurons in Diseased Basal Ganglia Commit Suicide?	502
BOX 14.4 OF SPECIAL INTEREST: Destruction and Stimulation: Useful Therapies for Brain Disorders	504
THE INITIATION OF MOVEMENT BY PRIMARY MOTOR CORTEX	505
The Input-Output Organization of M1	506
The Coding of Movement in M1	507
BOX 14.5 PATH OF DISCOVERY: Distributed Coding in the Superior Colliculus, by James T. McIlwain	510
<i>The Malleable Motor Map</i>	509
THE CEREBELLUM	510
BOX 14.6 OF SPECIAL INTEREST: Involuntary Movements—Normal and Abnormal	512
Anatomy of the Cerebellum	513
The Motor Loop through the Lateral Cerebellum	514
<i>Programming the Cerebellum</i>	515
CONCLUDING REMARKS	516

PART THREE The Brain and Behavior 519

CHAPTER FIFTEEN Chemical Control of the Brain and Behavior 521

INTRODUCTION 522

THE SECRETORY HYPOTHALAMUS 524

An Overview of the Hypothalamus 524

Homeostasis 524

Structure and Connections of the Hypothalamus 524

Pathways to the Pituitary 525

Hypothalamic Control of the Posterior Pituitary 525

Hypothalamic Control of the Anterior Pituitary 528

BOX 15.1 OF SPECIAL INTEREST: Stress and the Brain 531

THE AUTONOMIC NERVOUS SYSTEM 531

ANS Circuits 532

Sympathetic and Parasympathetic Divisions 533

The Enteric Division 535

Central Control of the ANS 537

Neurotransmitters and the Pharmacology of Autonomic Function 537

Preganglionic Neurotransmitters 537

Postganglionic Neurotransmitters 538

THE DIFFUSE MODULATORY SYSTEMS OF THE BRAIN 538

Anatomy and Functions of the Diffuse Modulatory Systems 539

BOX 15.2 OF SPECIAL INTEREST: You Eat What You Are 540

The Noradrenergic Locus Coeruleus 539

BOX 15.3 PATH OF DISCOVERY: Exploring the Central Noradrenergic Neurons, by Floyd Bloom 542

The Serotonergic Raphe Nuclei 541

The Dopaminergic Substantia Nigra and Ventral Tegmental Area 542

The Cholinergic Basal Forebrain and Brain Stem Complexes 545

Drugs and the Diffuse Modulatory Systems 546

Hallucinogens 546

Stimulants 546

CONCLUDING REMARKS 548

CHAPTER SIXTEEN Motivation 551

INTRODUCTION 552

THE HYPOTHALAMUS, HOMEOSTASIS, AND MOTIVATED BEHAVIOR 552

THE LONG-TERM REGULATION OF FEEDING BEHAVIOR 553

Energy Balance 553

Hormonal and Hypothalamic Regulation of Body Fat and Feeding 554

Body Fat and Food Consumption 554

BOX 16.1 OF SPECIAL INTEREST: The Starving Brains of the Obese 556

The Hypothalamus and Feeding 556

The Effects of Elevated Leptin Levels on the Hypothalamus 557

The Effects of Decreased Leptin Levels on the Hypothalamus 558

The Control of Feeding by Lateral Hypothalamic Peptides 560

THE SHORT-TERM REGULATION OF FEEDING BEHAVIOR 561

Appetite, Eating, Digestion, and Satiety 562

BOX 16.2 OF SPECIAL INTEREST: Marijuana and the Munchies 563

Ghrelin 564

Gastric Distension 564

Cholecystokinin 564

Insulin 564

BOX 16.3 OF SPECIAL INTEREST: Diabetes Mellitus and Insulin Shock 565

WHY DO WE EAT? 566

Reinforcement and Reward 566

BOX 16.4 OF SPECIAL INTEREST: Self-Stimulation of the Human Brain 567

The Role of Dopamine in Motivation 568

BOX 16.5 OF SPECIAL INTEREST: Dopamine and Addiction 569

BOX 16.6 PATH OF DISCOVERY: Learning to Crave, by Julie Kauer 572

Serotonin, Food, and Mood 571

OTHER MOTIVATED BEHAVIORS 571

Drinking 572

Temperature Regulation 575

CONCLUDING REMARKS 576**BOX 16.7 OF SPECIAL INTEREST: Neuroeconomics 577****CHAPTER SEVENTEEN Sex and the Brain 579****INTRODUCTION 580****SEX AND GENDER 580**

The Genetics of Sex 581

Sex Chromosome Abnormalities 582

Sexual Development and Differentiation 583

THE HORMONAL CONTROL OF SEX 584

The Principal Male and Female Hormones 584

The Control of Sex Hormones by the Pituitary and Hypothalamus 585

THE NEURAL BASIS OF SEXUAL BEHAVIORS 587

Reproductive Organs and Their Control 587

Mammalian Mating Strategies 590

The Neurochemistry of Reproductive Behavior 590

BOX 17.1 PATH OF DISCOVERY: Bonding with Voles, by Thomas Insel 592

Love, Bonding, and the Human Brain 594

WHY AND HOW MALE AND FEMALE BRAINS DIFFER 595

Sexual Dimorphisms of the Central Nervous System 596

Sexual Dimorphisms of Cognition 598

Sex Hormones, The Brain, and Behavior 599

*Masculinization of the Fetal Brain 599***BOX 17.2 OF SPECIAL INTEREST: Bird Songs and Bird Brains 601***Mismatches between Genetic Sex and Hormone Action 602*Direct Genetic Effects on Behavior and Sexual Differentiation
of the Brain 603**BOX 17.3 OF SPECIAL INTEREST: David Reimer and the Basis of
Gender Identity 604**

The Activational Effects of Sex Hormones 606

*Brain Changes Associated with Maternal and Paternal Behavior 606**Estrogen Effects on Neuron Function, Memory, and Disease 608*

Sexual Orientation 610

CONCLUDING REMARKS 612**CHAPTER EIGHTEEN Brain Mechanisms of Emotion 615****INTRODUCTION 616****EARLY THEORIES OF EMOTION 616**

The James–Lange Theory 617

The Cannon–Bard Theory 617

BOX 18.1 OF SPECIAL INTEREST: Butterflies in the Stomach 620

Implications of Unconscious Emotion 619

THE LIMBIC SYSTEM 621

Broca's Limbic Lobe 622

The Papez Circuit 622

BOX 18.2 OF SPECIAL INTEREST: Phineas Gage 624

Difficulties with the Concept of a Single System for Emotions 624

EMOTION THEORIES AND NEURAL REPRESENTATIONS 625

Basic Emotion Theories 626

Dimensional Emotion Theories 627

What is an Emotion? 628

**BOX 18.3 PATH OF DISCOVERY: Concepts and Names in Everyday Science,
by Antonio Damasio 629****FEAR AND THE AMYGDALA 630**

The Klüver–Bucy Syndrome 630

Anatomy of the Amygdala 631

Effects of Amygdala Stimulation and Lesions 632

A Neural Circuit for Learned Fear 633

ANGER AND AGGRESSION 635**The Amygdala and Aggression 635***Surgery to Reduce Human Aggression 636***BOX 18.4 OF SPECIAL INTEREST:** *The Frontal Lobotomy 637***Neural Components of Anger and Aggression Beyond the Amygdala 637***Anger, Aggression, and the Hypothalamus 638**The Midbrain and Aggression 639***Serotonergic Regulation of Anger and Aggression 640****CONCLUDING REMARKS 641****CHAPTER NINETEEN Brain Rhythms and Sleep 645****INTRODUCTION 646****THE ELECTROENCEPHALOGRAM 646****Recording Brain Waves 647****BOX 19.1 PATH OF DISCOVERY:** *The Puzzle of Brain Rhythms, by Stephanie R. Jones 650***EEG Rhythms 650****Mechanisms and Meanings of Brain Rhythms 653***The Generation of Synchronous Rhythms 653**Functions of Brain Rhythms 655***The Seizures of Epilepsy 655****SLEEP 658****The Functional States of the Brain 658****The Sleep Cycle 660****BOX 19.2 OF SPECIAL INTEREST:** *Walking, Talking, and Screaming in Your Sleep 661***Why Do We Sleep? 662****BOX 19.3 OF SPECIAL INTEREST:** *The Longest All-Nighter 664***Functions of Dreaming and REM Sleep 664****Neural Mechanisms of Sleep 666***Wakefulness and the Ascending Reticular Activating System 666***BOX 19.4 OF SPECIAL INTEREST:** *Narcolepsy 669**Falling Asleep and the Non-REM State 668**Mechanisms of REM Sleep 670**Sleep-Promoting Factors 671**Gene Expression during Sleeping and Waking 672***CIRCADIAN RHYTHMS 673****Biological Clocks 674****The Suprachiasmatic Nucleus: A Brain Clock 676****BOX 19.5 OF SPECIAL INTEREST:** *Mutant Hamster Clocks 678***SCN Mechanisms 679****CONCLUDING REMARKS 681****CHAPTER TWENTY Language 685****INTRODUCTION 686****WHAT IS LANGUAGE? 686****Human Sound and Speech Production 686****BOX 20.1 OF SPECIAL INTEREST:** *Thinking in Different Languages 688***Language in Animals 688****Language Acquisition 690****Genes Involved in Language 692***FOXP2 and Verbal Dyspraxia 692**Genetic Factors in Specific Language Impairment and Dyslexia 693***THE DISCOVERY OF SPECIALIZED LANGUAGE AREAS IN THE BRAIN 694****Broca's Area and Wernicke's Area 695****BOX 20.2 OF SPECIAL INTEREST:** *Assessing Hemispheric Language Dominance 696***LANGUAGE INSIGHTS FROM THE STUDY OF APHASIA 697****BOX 20.3 PATH OF DISCOVERY:** *Uncovering Language Areas of the Brain, by Nina Dronkers 698***Broca's Aphasia 699****Wernicke's Aphasia 700****The Wernicke–Geschwind Model of Language and Aphasia 701**

Conduction Aphasia	704
Aphasia in Bilinguals and Deaf People	705
ASYMMETRICAL LANGUAGE PROCESSING IN THE TWO CEREBRAL HEMISPHERES	706
Language Processing in Split-Brain Humans	707
Left Hemisphere Language Dominance	708
Language Functions of the Right Hemisphere	708
Anatomical Asymmetry and Language	709
LANGUAGE STUDIES USING BRAIN STIMULATION AND HUMAN BRAIN IMAGING	711
The Effects of Brain Stimulation on Language	711
Imaging of Language Processing in the Human Brain	713
BOX 20.4 OF SPECIAL INTEREST: Hearing Sight and Seeing Touch	714
CONCLUDING REMARKS	717
CHAPTER TWENTY-ONE The Resting Brain, Attention, and Consciousness	719
INTRODUCTION	720
RESTING STATE BRAIN ACTIVITY	720
The Brain's Default Mode Network	721
Functions of the Default Network	722
ATTENTION	723
BOX 21.1 OF SPECIAL INTEREST: Attention-Deficit Hyperactivity Disorder	724
Behavioral Consequences of Attention	725
Attention Enhances Visual Sensitivity	725
Attention Speeds Reaction Times	727
Physiological Effects of Attention	728
Functional MRI Imaging of Human Attention to Location	728
PET Imaging of Human Attention to Features	729
Attention Enhances Responses of Neurons in Parietal Cortex	731
Attention Focuses Receptive Fields in Area V4	733
Brain Circuits for the Control of Attention	734
The Pulvinar, a Subcortical Component	734
The Frontal Eye Fields, Eye Movements, and Attention	735
Directing Attention with Saliency and Priority Maps	736
A Priority Map in the Parietal Lobe	737
BOX 21.2 OF SPECIAL INTEREST: Hemispatial Neglect Syndrome	738
The Frontoparietal Attention Network	740
CONSCIOUSNESS	742
What Is Consciousness?	742
Neural Correlates of Consciousness	743
BOX 21.3 PATH OF DISCOVERY: Tracking the Neuronal Footprints of Consciousness, by Christof Koch	744
Neuronal Correlates of Alternating Perception in Binocular Rivalry	743
Visual Awareness and Human Brain Activity	746
Challenges in the Study of Consciousness	748
CONCLUDING REMARKS	749
CHAPTER TWENTY-TWO Mental Illness	751
INTRODUCTION	752
MENTAL ILLNESS AND THE BRAIN	752
Psychosocial Approaches to Mental Illness	753
Biological Approaches to Mental Illness	753
The Promise and Challenge of Molecular Medicine in Psychiatry	754
ANXIETY DISORDERS	756
A Description of Anxiety Disorders	756
Panic Disorder	757
Agoraphobia	757
BOX 22.1 OF SPECIAL INTEREST: Agoraphobia with Panic Attacks	758
Other Disorders Characterized by Increased Anxiety	757
Post-Traumatic Stress Disorder	757

Obsessive-Compulsive Disorder 757

Biological Bases of Anxiety Disorders 758

The Stress Response 759

Regulation of the HPA Axis by the Amygdala and Hippocampus 760

Treatments for Anxiety Disorders 761

Psychotherapy 761

Anxiolytic Medications 761

AFFECTIVE DISORDERS 763

A Description of Affective Disorders 763

Major Depression 763

Bipolar Disorder 764

BOX 22.2 **OF SPECIAL INTEREST:** *A Magical Orange Grove in a Nightmare* 765

Biological Bases of Affective Disorders 764

The Monoamine Hypothesis 764

The Diathesis–Stress Hypothesis 766

Anterior Cingulate Cortex Dysfunction 767

Treatments for Affective Disorders 767

Electroconvulsive Therapy 768

Psychotherapy 768

Antidepressants 768

Lithium 770

Deep Brain Stimulation 771

BOX 22.3 **PATH OF DISCOVERY:** *Tuning Depression Circuits*, by Helen Mayberg 772

SCHIZOPHRENIA 771

A Description of Schizophrenia 771

Biological Bases of Schizophrenia 774

Genes and the Environment 774

The Dopamine Hypothesis 775

The Glutamate Hypothesis 777

Treatments for Schizophrenia 779

CONCLUDING REMARKS 779

PART FOUR The Changing Brain 781

CHAPTER TWENTY-THREE Wiring the Brain 783

INTRODUCTION 784

THE GENESIS OF NEURONS 785

Cell Proliferation 785

BOX 23.1 **OF SPECIAL INTEREST:** *Neurogenesis in Adult Humans* 787

Cell Migration 788

Cell Differentiation 789

Differentiation of Cortical Areas 791

BOX 23.2 **PATH OF DISCOVERY:** *Making a Map of the Mind*, by Pasko Rakic 792

THE GENESIS OF CONNECTIONS 795

The Growing Axon 796

Axon Guidance 797

Guidance Cues 797

Establishing Topographic Maps 799

BOX 23.3 **OF SPECIAL INTEREST:** *Why Our CNS Axons Don't Regenerate* 800

Synapse Formation 801

THE ELIMINATION OF CELLS AND SYNAPSES 802

BOX 23.4 **OF SPECIAL INTEREST:** *The Mystery of Autism* 803

Cell Death 803

Changes in Synaptic Capacity 804

ACTIVITY-DEPENDENT SYNAPTIC REARRANGEMENT 805

Synaptic Segregation 806

Segregation of Retinal Inputs to the LGN 806

Segregation of LGN Inputs in the Striate Cortex 808

BOX 23.5 **BRAIN FOOD:** *Three-Eyed Frogs, Ocular Dominance Columns, and Other Oddities* 808

BOX 23.6 **BRAIN FOOD:** *The Critical Period Concept* 810

Synaptic Convergence 809
 Synaptic Competition 811
 Modulatory Influences 812

ELEMENTARY MECHANISMS OF CORTICAL SYNAPTIC PLASTICITY 814

Excitatory Synaptic Transmission in the Immature Visual System 815
 Long-Term Synaptic Potentiation 815
 Long-Term Synaptic Depression 817

WHY CRITICAL PERIODS END 818

CONCLUDING REMARKS 819

CHAPTER TWENTY-FOUR Memory Systems 823

INTRODUCTION 824

TYPES OF MEMORY AND AMNESIA 824

Declarative and Nondeclarative Memory 824

BOX 24.1 OF SPECIAL INTEREST: Extraordinary Memory 826

Types of Procedural Memory 825

Nonassociative Learning 827

Associative Learning 827

Types of Declarative Memory 828

Amnesia 829

WORKING MEMORY 830

The Prefrontal Cortex and Working Memory 831

Imaging Working Memory in the Human Brain 832

Area LIP and Working Memory 833

DECLARATIVE MEMORY 835

The Neocortex and Declarative Memory 835

Hebb and the Cell Assembly 836

Studies Implicating the Medial Temporal Lobes 837

Anatomy of the Medial Temporal Lobe 838

Electrical Stimulation of the Human Temporal Lobes 839

Neural Recordings from the Human Medial Temporal Lobe 840

Temporal Lobe Amnesia 841

The Case of H.M.: Temporal Lobectomy and Amnesia 841

An Animal Model of Human Amnesia 843

BOX 24.2 OF SPECIAL INTEREST: Korsakoff's Syndrome
 and the Case of N.A. 845

Memory Functions of the Hippocampal System 846

The Effects of Hippocampal Lesions in Rats 846

Spatial Memory, Place Cells, and Grid Cells 847

BOX 24.3 PATH OF DISCOVERY: How the Brain Makes Maps, by Edvard
 and May-Britt Moser 850

Hippocampal Functions Beyond Spatial Memory 852

Consolidating Memories and Retaining Engrams 853

Standard and Multiple Trace Models of Consolidation 854

Reconsolidation 856

BOX 24.4 OF SPECIAL INTEREST: Introducing False Memories
 and Erasing Bad Memories 858

PROCEDURAL MEMORY 857

The Striatum and Procedural Memory in Rodents 857

Habit Learning in Humans and Nonhuman Primates 861

CONCLUDING REMARKS 862

CHAPTER TWENTY-FIVE Molecular Mechanisms of Learning and Memory 865

INTRODUCTION 866

MEMORY ACQUISITION 867

Cellular Reports of Memory Formation 867

Distributed Memory Storage 869

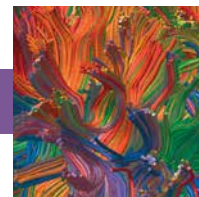
BOX 25.1 PATH OF DISCOVERY: What Attracted Me to the Study of Learning and
 Memory in *Aplysia*? by Eric Kandel 871

Strengthening Synapses 874

Anatomy of the Hippocampus 874

<i>Properties of LTP in CA1</i>	875
<i>Mechanisms of LTP in CA1</i>	877
BOX 25.2 BRAIN FOOD: Synaptic Plasticity: Timing Is Everything	878
Weakening Synapses	880
BOX 25.3 PATH OF DISCOVERY: Memories of Memory, by Leon Cooper	880
BOX 25.4 BRAIN FOOD: The Wide World of Long-Term Synaptic Depression	883
<i>Mechanisms of LTD in CA1</i>	882
<i>Glutamate Receptor Trafficking</i>	884
LTP, LTD, and Memory	885
BOX 25.5 OF SPECIAL INTEREST: Memory Mutants	888
Synaptic Homeostasis	889
<i>Metaplasticity</i>	889
<i>Synaptic Scaling</i>	891
MEMORY CONSOLIDATION	891
Persistently Active Protein Kinases	892
<i>CaMKII</i>	892
<i>Protein Kinase M Zeta</i>	893
Protein Synthesis and Memory Consolidation	893
<i>Synaptic Tagging and Capture</i>	894
<i>CREB and Memory</i>	894
<i>Structural Plasticity and Memory</i>	896
CONCLUDING REMARKS	897

LIST OF BOXES



BRAIN FOOD

Expressing One's Mind in the Post-Genomic Era 33
Understanding Neuronal Structure and
Function with Incredible Cre 50
A Review of Moles and Molarity 65
The Nernst Equation 70
The Goldman Equation 73
Methods of Recording Action Potentials 83
The Patch-Clamp Method 95
How to SNARE a Vesicle 125
Reversal Potentials 127
Pumping Ions and Transmitters 154
Magnetic Resonance Imaging 189
PET and fMRI 190
Cortical Organization Revealed by Optical
and Calcium Imaging 350
Lateral Inhibition 429
Three-Eyed Frogs, Ocular Dominance Columns,
and Other Oddities 808
The Critical Period Concept 810
Synaptic Plasticity: Timing Is Everything 878
The Wide World of Long-Term Synaptic
Depression 883

OF SPECIAL INTEREST

Advances in Microscopy 28
Alzheimer's Disease and the Neuronal
Cytoskeleton 40
Hitching a Ride with Retrograde Transport 45
Intellectual Disability and Dendritic Spines 47
Death by Lethal Injection 78
Local Anesthesia 102
Multiple Sclerosis, a Demyelinating Disease 103
The Eclectic Electric Behavior of Neurons 106
Otto Loewi's Dream 111
Bacteria, Spiders, Snakes, and People 131
Startling Mutations and Poisons 137
This Is Your Brain on Endocannabinoids 161
Exciting Poisons: Too Much of a Good Thing 167
Water on the Brain 187
Nutrition and the Neural Tube 194
Strange Tastes: Fat, Starch, Carbonation,
Calcium, Water? 268
Memories of a Very Bad Meal 276
Human Pheromones? 279
Demonstrating the Blind Regions of Your Eye 298
Eye Disorders 300
Vision Correction 302
The Genetics of Color Vision 317

David and Goliath 337
The Magic of Seeing in 3D 364
Ultrasound and Infrasound 372
The Deaf Shall Hear: Cochlear Implants 382
Hearing with Noisy Ears 387
How Does Auditory Cortex Work? Ask
a Specialist 400
Auditory Disorders and Their Treatments 402
Herpes, Shingles, and Dermatomes 426
The Misery of Life without Pain 438
Hot and Spicy 440
Pain and the Placebo Effect 448
ALS: Glutamate, Genes, and Gehrig 463
Myasthenia Gravis 464
Duchenne Muscular Dystrophy 468
Paresis, Paralysis, Spasticity, and Babinski 488
Behavioral Neurophysiology 495
Do Neurons in Diseased Basal Ganglia
Commit Suicide? 502
Destruction and Stimulation: Useful Therapies
for Brain Disorders 504
Involuntary Movements—Normal and Abnormal 512
Stress and the Brain 531
You Eat What You Are 540
The Starving Brains of the Obese 556
Marijuana and the Munchies 563
Diabetes Mellitus and Insulin Shock 565
Self-Stimulation of the Human Brain 567
Dopamine and Addiction 569
Neuroeconomics 577
Bird Songs and Bird Brains 601
David Reimer and the Basis of Gender Identity 604
Butterflies in the Stomach 620
Phineas Gage 624
The Frontal Lobotomy 637
Walking, Talking, and Screaming in Your Sleep 661
The Longest All-Nighter 664
Narcolepsy 669
Mutant Hamster Clocks 678
Thinking in Different Languages 688
Assessing Hemispheric Language Dominance 696
Hearing Sight and Seeing Touch 714
Attention-Deficit Hyperactivity Disorder 724
Hemispacial Neglect Syndrome 738
Agoraphobia with Panic Attacks 758
A Magical Orange Grove in a Nightmare 765
Neurogenesis in Adult Humans 787
Why Our CNS Axons Don't Regenerate 800
The Mystery of Autism 803

Extraordinary Memory 826
Korsakoff's Syndrome and the Case of N.A. 845
Introducing False Memories and
Erasing Bad Memories 858
Memory Mutants 888

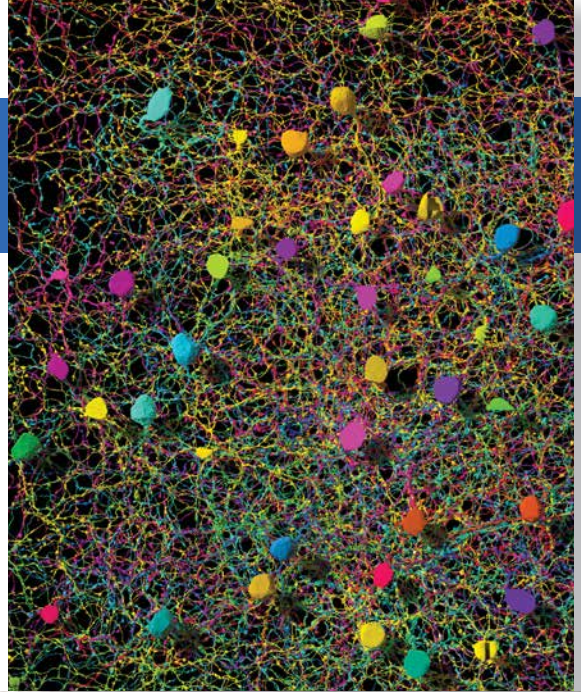
PATH OF DISCOVERY

Gene Targeting in Mice,
by Mario Capecchi 34
Feeling Around Inside Ion Channels in the Dark,
by Chris Miller 76
The Discovery of the Channelrhodopsins,
by Georg Nagel 86
For the Love of Dendritic Spines,
by Kristen M. Harris 118
Finding Opiate Receptors,
by Solomon H. Snyder 152
Connecting with the Connectome,
by Sebastian Seung 212
Channels of Vision and Smell,
by Geoffrey Gold 284
Seeing Through the Photoreceptor Mosaic,
by David Williams 308
Finding Faces in the Brain,
by Nancy Kanwisher 360
Capturing the Beat,
by Donata Oertel 394
Cortical Barrels,
by Thomas Woolsey 434

Nerve Regeneration Does Not Ensure Full Recovery,
by Timothy C. Cope 472
Distributed Coding in the Superior Colliculus,
by James T. McIlwain 510
Exploring the Central Noradrenergic Neurons,
by Floyd Bloom 542
Learning to Crave,
by Julie Kauer 572
Bonding with Voles,
by Thomas Insel 592
Concepts and Names in Everyday Science,
by Antonio Damasio 629
The Puzzle of Brain Rhythms,
by Stephanie R. Jones 650
Uncovering Language Areas of the Brain,
by Nina Dronkers 698
Tracking the Neuronal Footprints of Consciousness,
by Christof Koch 744
Tuning Depression Circuits,
by Helen Mayberg 772
Making a Map of the Mind,
by Pasko Rakic 792
How the Brain Makes Maps,
by Edvard and May-Britt Moser 850
What Attracted Me to the Study of Learning
and Memory in *Aplysia*?
by Eric Kandel 871
Memories of Memory,
by Leon Cooper 880

PART ONE

Foundations



CHAPTER 1

Neuroscience: Past, Present, and Future 3

CHAPTER 2

Neurons and Glia 23

CHAPTER 3

The Neuronal Membrane at Rest 55

CHAPTER 4

The Action Potential 81

CHAPTER 5

Synaptic Transmission 109

CHAPTER 6

Neurotransmitter Systems 143

CHAPTER 7

The Structure of the Nervous System 179

Appendix: An Illustrated Guide to Human Neuroanatomy 219

CHAPTER ONE

Neuroscience: Past, Present, and Future

INTRODUCTION

THE ORIGINS OF NEUROSCIENCE

- Views of the Brain in Ancient Greece
- Views of the Brain During the Roman Empire
- Views of the Brain from the Renaissance to the Nineteenth Century
- Nineteenth-Century Views of the Brain
 - Nerves as Wires*
 - Localization of Specific Functions to Different Parts of the Brain*
 - The Evolution of Nervous Systems*
 - The Neuron: The Basic Functional Unit of the Brain*

NEUROSCIENCE TODAY

Levels of Analysis

- Molecular Neuroscience*
- Cellular Neuroscience*
- Systems Neuroscience*
- Behavioral Neuroscience*
- Cognitive Neuroscience*

Neuroscientists

The Scientific Process

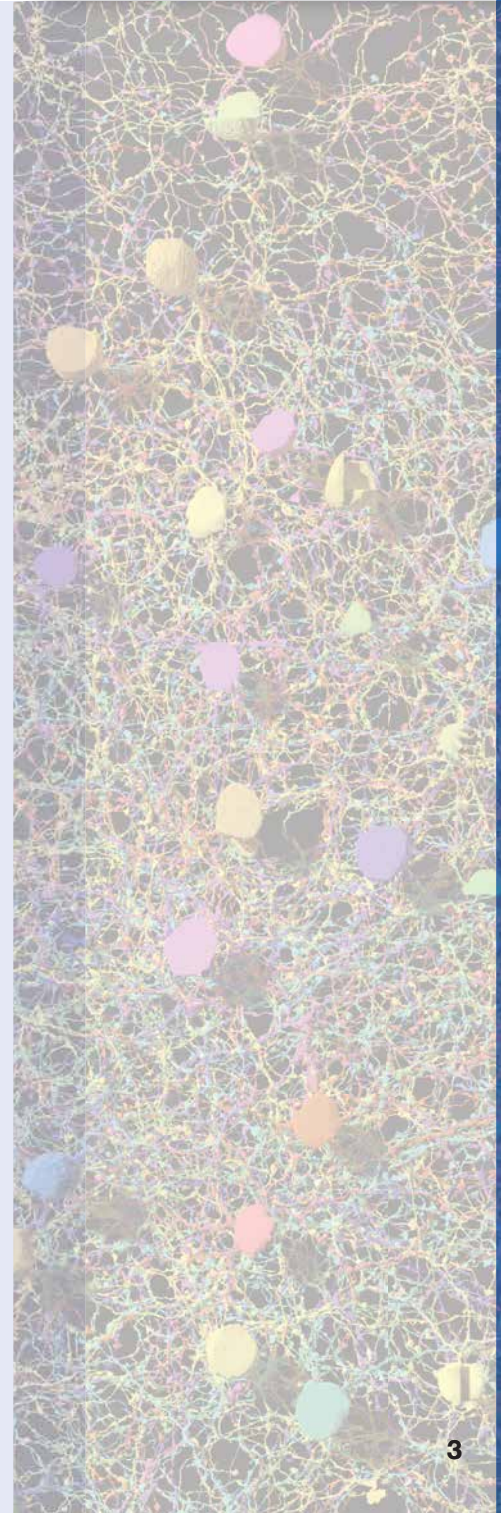
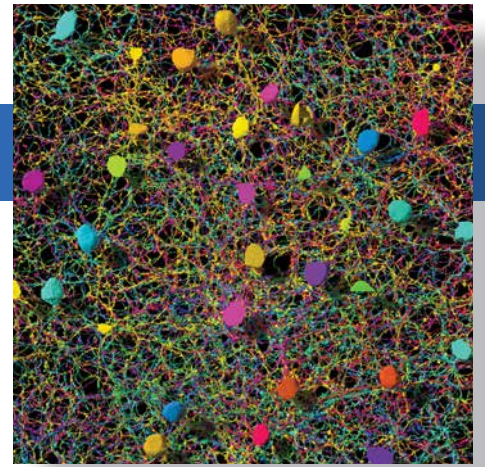
- Observation*
- Replication*
- Interpretation*
- Verification*

The Use of Animals in Neuroscience Research

- The Animals*
- Animal Welfare*
- Animal Rights*

The Cost of Ignorance: Nervous System Disorders

CONCLUDING REMARKS



INTRODUCTION

Men ought to know that from nothing else but the brain come joys, delights, laughter and sports, and sorrows, griefs, despondency, and lamentations. And by this, in an especial manner, we acquire wisdom and knowledge, and see and hear and know what are foul and what are fair, what are bad and what are good, what are sweet and what are unsavory. . . . And by the same organ we become mad and delirious, and fears and terrors assail us. . . . All these things we endure from the brain when it is not healthy. . . . In these ways I am of the opinion that the brain exercises the greatest power in the man.

—Hippocrates, *On the Sacred Disease* (Fourth century B.C.E.)

It is human nature to be curious about how we see and hear; why some things feel good and others hurt; how we move; how we reason, learn, remember, and forget; and the nature of anger and madness. Neuroscience research is unraveling these mysteries, and the conclusions of this research are the subject of this textbook.

The word “neuroscience” is young. The Society for Neuroscience, an association of professional neuroscientists, was founded only relatively recently in 1970. The study of the brain, however, is as old as science itself. Historically, the scientists who devoted themselves to an understanding of the nervous system came from different scientific disciplines: medicine, biology, psychology, physics, chemistry, mathematics. The neuroscience revolution occurred when scientists realized that the best hope for understanding the workings of the brain would come from an interdisciplinary approach, a combination of traditional approaches to yield a new synthesis, a new perspective. Most people involved in the scientific investigation of the nervous system today regard themselves as neuroscientists. Indeed, while the course you are now taking may be sponsored by the psychology or biology department at your university or college and may be called biopsychology or neurobiology, you can bet that your instructor is a neuroscientist.

The Society for Neuroscience is one of the largest and fastest growing associations of professional scientists. Far from being overly specialized, the field is as broad as nearly all of natural science, with the nervous system serving as the common point of focus. Understanding how the brain works requires knowledge about many things, from the structure of the water molecule to the electrical and chemical properties of the brain to why Pavlov’s dog salivated when a bell rang. This book explores the brain with this broad perspective.

We begin the adventure with a brief tour of neuroscience. What have scientists thought about the brain over the ages? Who are the neuroscientists of today, and how do they approach studying the brain?

THE ORIGINS OF NEUROSCIENCE

You probably already know that the nervous system—the brain, spinal cord, and nerves of the body—is crucial for life and enables you to sense, move, and think. How did this view arise?

Evidence suggests that even our prehistoric ancestors appreciated that the brain was vital to life. The archeological record includes many hominid skulls, dating back a million years and more, that bear signs of fatal cranial damage likely inflicted by other hominids. As early as 7000 years ago, people were boring holes in each other’s skulls (a process called

trepanation), evidently with the aim not to kill but to cure (Figure 1.1). These skulls show signs of healing after the operation, indicating that this procedure had been carried out on live subjects rather than being a ritual conducted after death. Some individuals apparently survived multiple skull surgeries. What those early surgeons hoped to accomplish is not clear, although it has been speculated that this procedure may have been used to treat headaches or mental disorders, perhaps by giving the evil spirits an escape route.

Recovered writings from the physicians of ancient Egypt, dating back almost 5000 years, indicate that they were well aware of many symptoms of brain damage. However, it is also very clear that the heart, not the brain, was considered to be the seat of the soul and the repository of memories. Indeed, while the rest of the body was carefully preserved for the afterlife, the brain of the deceased was simply scooped out through the nostrils and discarded! The view that the heart was the seat of consciousness and thought was not seriously challenged until the time of Hippocrates.

Views of the Brain in Ancient Greece

Consider the idea that the different parts of your body look different because they serve different purposes. The structures of the feet and hands are very different, for example, because they perform very different functions: We walk on our feet and manipulate objects with our hands. Thus, there appears to be a very clear *correlation between structure and function*. Differences in appearance predict differences in function.

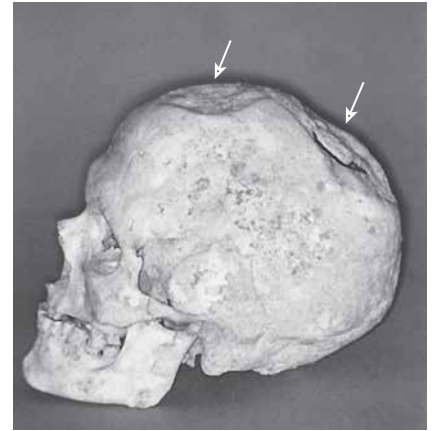
What can we glean about function from the structure of the head? Quick inspection and a few simple experiments (like closing your eyes) reveal that the head is specialized for sensing the environment with the eyes and ears, nose, and tongue. Even crude dissection can trace the nerves from these organs through the skull into the brain. What would you conclude about the brain from these observations?

If your answer is that the brain is the organ of sensation, then you have reached the same conclusion as several Greek scholars of the fourth century B.C.E. The most influential scholar was Hippocrates (460–379 B.C.E.), the father of Western medicine, who believed that the brain was not only involved in sensation but was also the seat of intelligence.

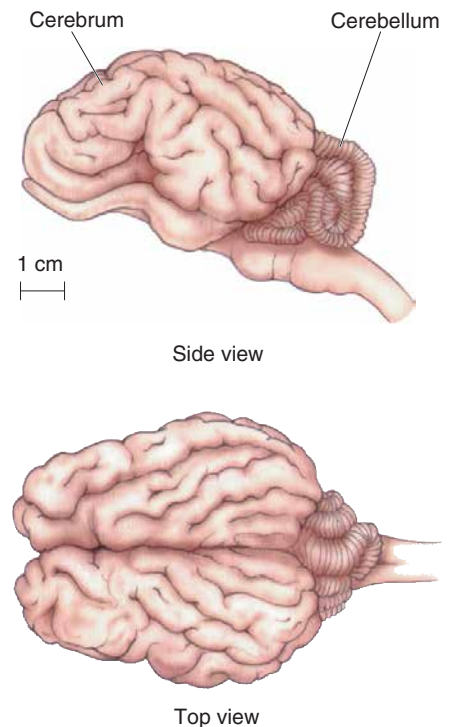
This view was not universally accepted, however. The famous Greek philosopher Aristotle (384–322 B.C.E.) clung to the belief that the heart was the center of intellect. What function did Aristotle reserve for the brain? He believed it was a radiator for cooling blood that was overheated by the seething heart. The rational temperament of humans was thus explained by the large cooling capacity of our brain.

Views of the Brain During the Roman Empire

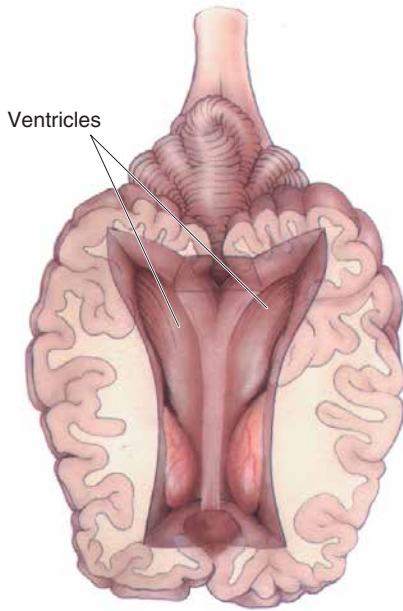
The most important figure in Roman medicine was the Greek physician and writer Galen (130–200 C.E.), who embraced the Hippocratic view of brain function. As physician to the gladiators, he must have witnessed the unfortunate consequences of spine and brain injuries. However, Galen's opinions about the brain were probably influenced more by his many careful animal dissections. Figure 1.2 is a drawing of the brain of a sheep, one of Galen's favorite subjects. Two major parts are evident: the *cerebrum* in the front and the *cerebellum* in the back. (The structure of the brain is described in Chapter 7.) Just as we can deduce function



▲ **FIGURE 1.1**
Evidence of prehistoric brain surgery. This skull of a man over 7000 years old was surgically opened while he was still alive. The arrows indicate two sites of trepanation. (Source: Alt et al., 1997, Fig. 1a.)



▲ **FIGURE 1.2**
The brain of a sheep. Notice the location and appearance of the cerebrum and the cerebellum.



▲ **FIGURE 1.3**
A dissected sheep brain showing the ventricles.

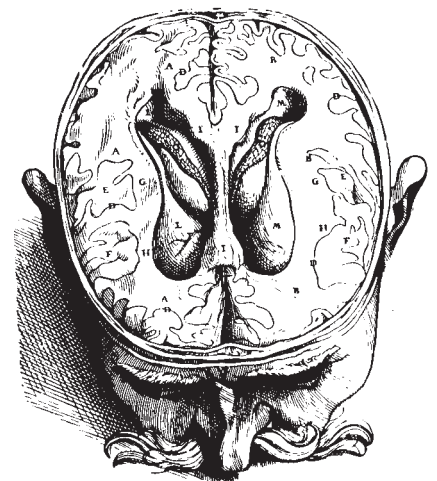
from the structure of the hands and feet, Galen tried to deduce function from the structure of the cerebrum and the cerebellum. Poking the freshly dissected brain with a finger reveals the cerebellum is rather hard and the cerebrum rather soft. From this observation, Galen suggested that the cerebrum must receive sensations while the cerebellum must command the muscles. Why such a distinction? He recognized that to form memories, sensations must be imprinted in the brain. Naturally, this must occur in the doughy cerebrum.

As improbable as his reasoning may seem, Galen's deductions were not that far from the truth. The cerebrum, in fact, is largely concerned with sensation and perception, and the cerebellum is primarily a movement control center. Moreover, the cerebrum is a repository of memory. We will see that this is not the only example in the history of neuroscience in which the right general conclusions were reached for the wrong reasons.

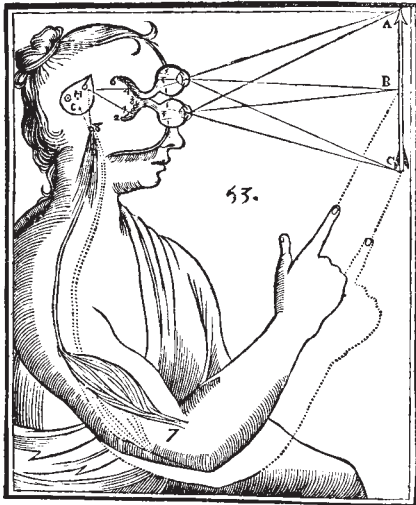
How does the brain receive sensations and move the limbs? Galen cut open the brain and found that it is hollow (Figure 1.3). In these hollow spaces, called *ventricles* (like the similar chambers in the heart), there is fluid. To Galen, this discovery fit perfectly with the prevailing theory that the body functioned according to a balance of four vital fluids, or humors. Sensations were registered and movements initiated by the movement of humors to or from the brain ventricles via the nerves, which were believed to be hollow tubes, like the blood vessels.

Views of the Brain from the Renaissance to the Nineteenth Century

Galen's view of the brain prevailed for almost 1500 years. During the Renaissance, the great anatomist Andreas Vesalius (1514–1564) added more detail to the structure of the brain (Figure 1.4). However, the ventricular theory of brain function remained essentially unchallenged. Indeed, the whole concept was strengthened in the early seventeenth century, when French inventors built hydraulically controlled mechanical devices. These devices supported the notion that the brain could be machinelike in its function: Fluid forced out of the ventricles through the nerves might literally “pump you up” and cause the movement of the limbs. After all, don't the muscles bulge when they contract?



► **FIGURE 1.4**
Human brain ventricles depicted during the Renaissance. This drawing is from *De humani corporis fabrica* by Vesalius (1543). The subject was probably a decapitated criminal. Great care was taken to be anatomically correct in depicting the ventricles. (Source: Finger, 1994, Fig. 2.8.)



◀ **FIGURE 1.5**

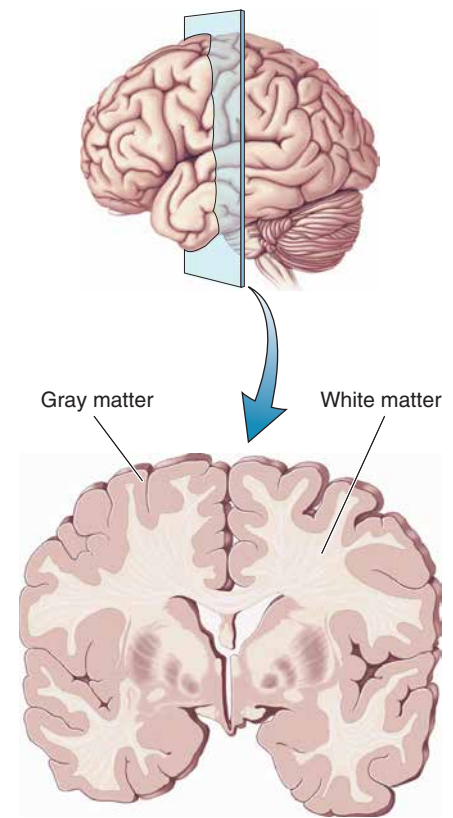
The brain according to Descartes.

This drawing appeared in a 1662 publication by Descartes, who thought that hollow nerves from the eyes projected to the brain ventricles. The mind influenced the motor response by controlling the pineal gland (H), which worked like a valve to control the movement of animal spirits through the nerves that inflated the muscles. (Source: Finger, 1994, Fig. 2.16.)

A chief advocate of this fluid-mechanical theory of brain function was the French mathematician and philosopher René Descartes (1596–1650). Although he thought this theory could explain the brain and behavior of other animals, Descartes believed it could not possibly account for the full range of *human* behavior. He reasoned that unlike other animals, people possess intellect and a God-given soul. Thus, Descartes proposed that brain mechanisms control only human behavior that is like that of the beasts. Uniquely human mental capabilities exist outside the brain in the “mind.” Descartes believed that the mind is a spiritual entity that receives sensations and commands movements by communicating with the machinery of the brain via the pineal gland (Figure 1.5). Today, some people still believe that there is a “mind-brain problem,” that somehow the human mind is distinct from the brain. However, as we shall see in Part III, modern neuroscience research supports a different conclusion: The mind has a physical basis, which is the brain.

Fortunately, other scientists during the seventeenth and eighteenth centuries broke away from the traditional focus on the ventricles and began examining the brain’s substance more closely. They observed, for example, two types of brain tissue: the *gray matter* and the *white matter* (Figure 1.6). What structure–function relationship did they propose? White matter, because it was continuous with the nerves of the body, was correctly believed to contain the fibers that bring information to and from the gray matter.

By the end of the eighteenth century, the nervous system had been completely dissected and its gross anatomy described in detail. Scientists recognized that the nervous system has a central division, consisting of the brain and spinal cord, and a peripheral division, consisting of the network of nerves that course through the body (Figure 1.7). An important breakthrough in neuroanatomy came with the observation that the same general pattern of bumps (called *gyri*) and grooves (called *sulci* and *fissures*) can be identified on the surface of the brain in every individual (Figure 1.8). This pattern, which enables the parcelling of the cerebrum into *lobes*, led to speculation that different functions might be localized to the different bumps on the brain. The stage was now set for the era of cerebral localization.



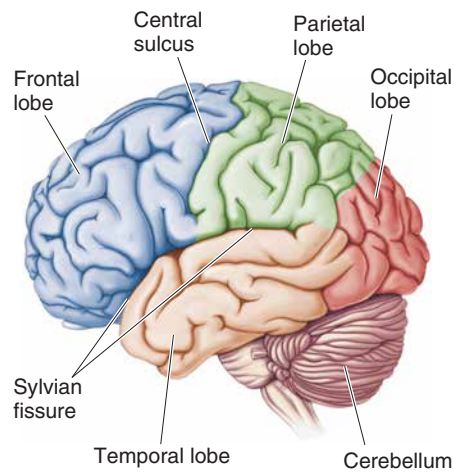
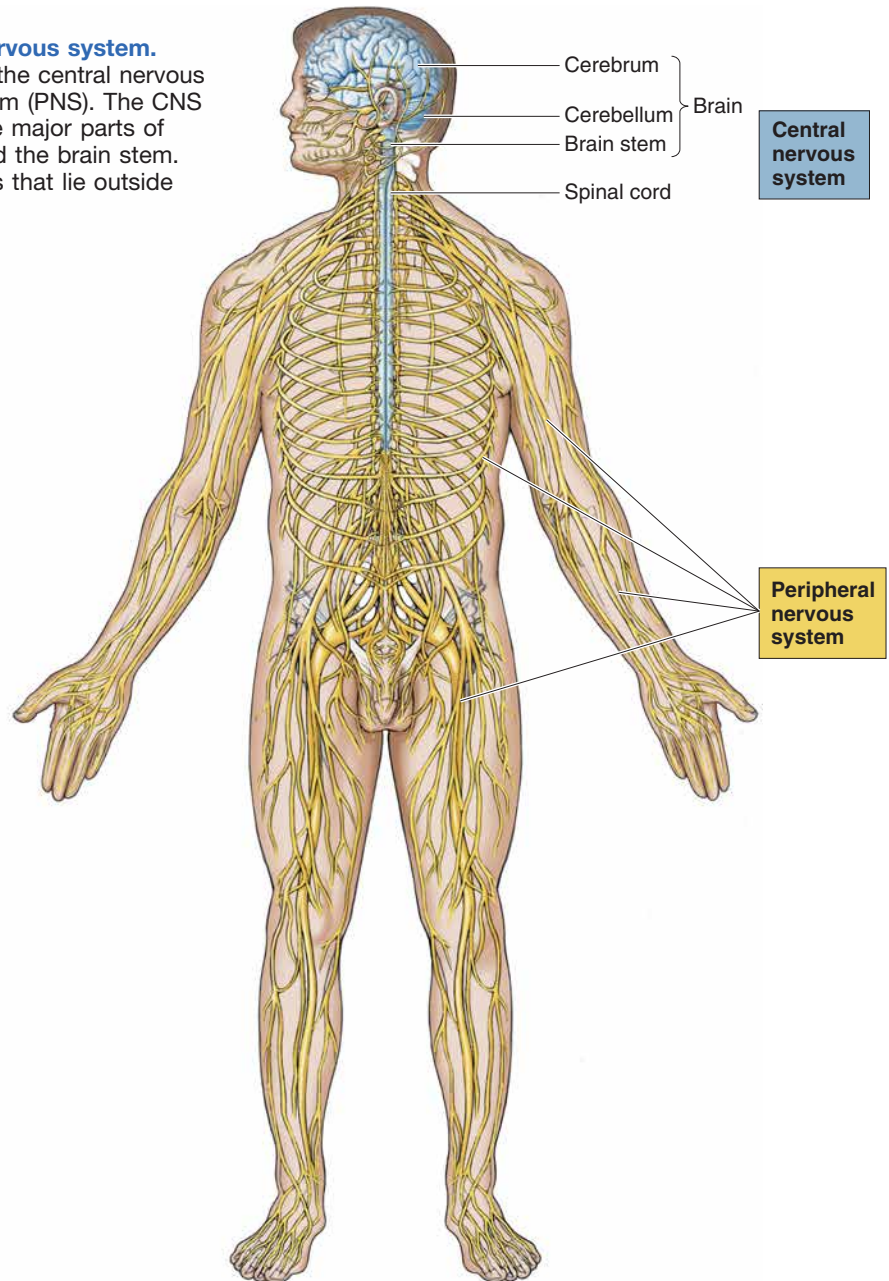
▲ **FIGURE 1.6**

White matter and gray matter.

The human brain has been cut open to reveal these two types of tissue.

► **FIGURE 1.7****The basic anatomical subdivisions of the nervous system.**

The nervous system consists of two divisions, the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS consists of the brain and spinal cord. The three major parts of the brain are the cerebrum, the cerebellum, and the brain stem. The PNS consists of the nerves and nerve cells that lie outside the brain and spinal cord.

▲ **FIGURE 1.8**

The lobes of the cerebrum. Notice the deep Sylvian fissure, dividing the frontal lobe from the temporal lobe, and the central sulcus, dividing the frontal lobe from the parietal lobe. The occipital lobe lies at the back of the brain. These landmarks can be found on all human brains.

Nineteenth-Century Views of the Brain

Let's review how the nervous system was understood at the end of the eighteenth century:

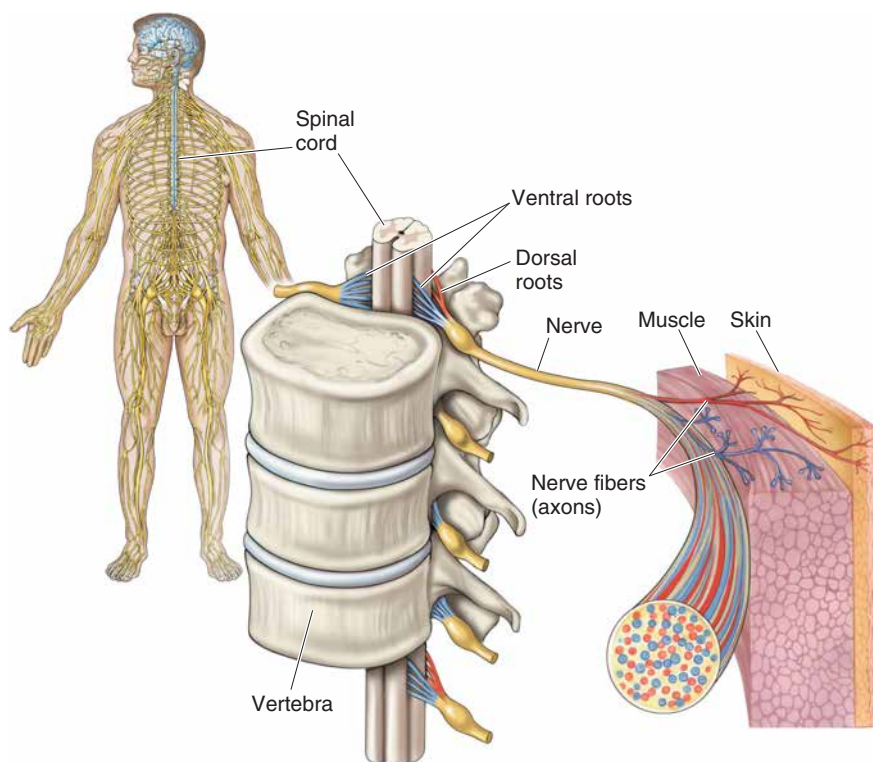
- Injury to the brain can disrupt sensations, movement, and thought and can cause death.
- The brain communicates with the body via the nerves.
- The brain has different identifiable parts, which probably perform different functions.
- The brain operates like a machine and follows the laws of nature.

During the next 100 years, more would be learned about the function of the brain than had been learned in all of previous recorded history. This work provided the solid foundation on which modern neuroscience rests. Now we'll look at four key insights gained during the nineteenth century.

Nerves as Wires. In 1751, Benjamin Franklin published a pamphlet titled *Experiments and Observations on Electricity*, which heralded a new understanding of electrical phenomena. By the turn of the century, Italian scientist Luigi Galvani and German biologist Emil du Bois-Reymond had shown that muscles can be caused to twitch when nerves are stimulated electrically and that the brain itself can generate electricity. These discoveries finally displaced the notion that nerves communicate with the brain by the movement of fluid. The new concept was that the nerves are “wires” that conduct electrical signals to and from the brain.

Unresolved was whether the signals to the muscles causing movement use the same wires as those that register sensations from the skin. Bidirectional communication along the same wires was suggested by the observation that when a nerve in the body is cut, there is usually a loss of both sensation and movement in the affected region. However, it was also known that within each nerve of the body there are many thin filaments, or *nerve fibers*, each one of which could serve as an individual wire carrying information in a different direction.

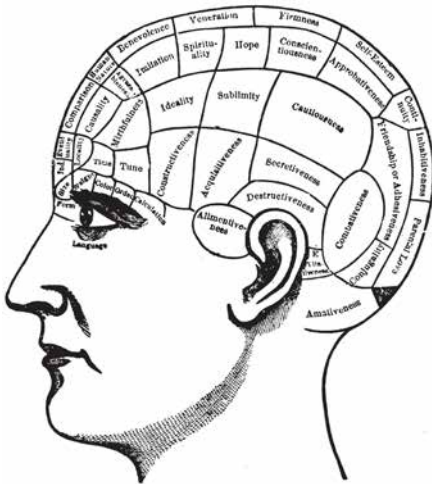
This question was answered around 1810 by Scottish physician Charles Bell and French physiologist François Magendie. A curious anatomical fact is that just before the nerves attach to the spinal cord, the fibers divide into two branches, or roots. The dorsal root enters toward the back of the spinal cord, and the ventral root enters toward the front (Figure 1.9). Bell tested the possibility that these two spinal roots carry information in different directions by cutting each root separately and observing the consequences in experimental animals. He found that cutting only the ventral roots caused muscle paralysis. Later, Magendie was able to show that the dorsal roots carry sensory information into the spinal cord. Bell and Magendie concluded that within each nerve is a mixture of many wires, some of which bring information into the brain and spinal cord and others that send information out to the muscles. In each



◀ **FIGURE 1.9**

Spinal nerves and spinal nerve roots.

Thirty-one pairs of nerves leave the spinal cord to supply the skin and the muscles. Cutting a spinal nerve leads to a loss of sensation and a loss of movement in the affected region of the body. Incoming sensory fibers (red) and outgoing motor fibers (blue) divide into spinal roots where the nerves attach to the spinal cord. Bell and Magendie found that the ventral roots contain only motor fibers and the dorsal roots contain only sensory fibers.



▲ **FIGURE 1.10**

A phrenological map. According to Gall and his followers, different behavioral traits could be related to the size of different parts of the skull. (Source: Clarke and O'Malley, 1968, Fig. 118.)



▲ **FIGURE 1.11**

Paul Broca (1824–1880). By carefully studying the brain of a man who had lost the faculty of speech after a brain lesion (see Figure 1.12), Broca became convinced that different functions could be localized to different parts of the cerebrum. (Source: Clarke and O'Malley, 1968, Fig. 121.)

sensory and motor nerve fiber, transmission is strictly one-way. The two kinds of fibers are bundled together for most of their length, but they are anatomically segregated where they enter or exit the spinal cord.

Localization of Specific Functions to Different Parts of the Brain. If different functions are localized in different spinal roots, then perhaps different functions are also localized in different parts of the brain. In 1811, Bell proposed that the origin of the motor fibers is the cerebellum and the destination of the sensory fibers is the cerebrum.

How would you test this proposal? One way is to use the same approach that Bell and Magendie employed to identify the functions of the spinal roots: to destroy these parts of the brain and test for sensory and motor deficits. This approach, in which parts of the brain are systematically destroyed to determine their function, is called the *experimental ablation method*. In 1823, the esteemed French physiologist Marie-Jean-Pierre Flourens used this method in a variety of animals (particularly birds) to show that the cerebellum does indeed play a role in the coordination of movement. He also concluded that the cerebrum is involved in sensation and perception, as Bell and Galen before him had suggested. Unlike his predecessors, however, Flourens provided solid experimental support for his conclusions.

What about all those bumps on the brain's surface? Do they perform different functions as well? The idea that they do was irresistible to a young Austrian medical student named Franz Joseph Gall. Believing that bumps on the surface of the skull reflect bumps on the surface of the brain, Gall proposed in 1809 that the propensity for certain personality traits, such as generosity, secretiveness, and destructiveness, could be related to the dimensions of the head (Figure 1.10). To support his claim, Gall and his followers collected and carefully measured the skulls of hundreds of people representing an extensive range of personality types, from the very gifted to the criminally insane. This new "science" of correlating the structure of the head with personality traits was called *phrenology*. Although the claims of the phrenologists were never taken seriously by the mainstream scientific community, they did capture the popular imagination of the time. In fact, a textbook on phrenology published in 1827 sold over 100,000 copies.

One of the most vociferous critics of phrenology was Flourens, the same man who had shown experimentally that the cerebellum and cerebrum perform different functions. His grounds for criticism were sound. For one thing, the shape of the skull is not correlated with the shape of the brain. In addition, Flourens performed experimental ablations showing that particular traits are not isolated to the portions of the cerebrum specified by phrenology. Flourens also maintained, however, that all regions of the cerebrum participate equally in all cerebral functions, a conclusion later shown to be erroneous.

The person usually credited with tilting the scales of scientific opinion firmly toward localization of functions in the cerebrum was French neurologist Paul Broca (Figure 1.11). Broca was presented with a patient who could understand language but could not speak. After the man's death in 1861, Broca carefully examined his brain and found a lesion in the left frontal lobe (Figure 1.12). Based on this case and several others like it, Broca concluded that this region of the human cerebrum was specifically responsible for the production of speech.

Solid experimental support for cerebral localization in animals quickly followed. German physiologists Gustav Fritsch and Eduard Hitzig showed in 1870 that applying small electrical currents to a circumscribed region

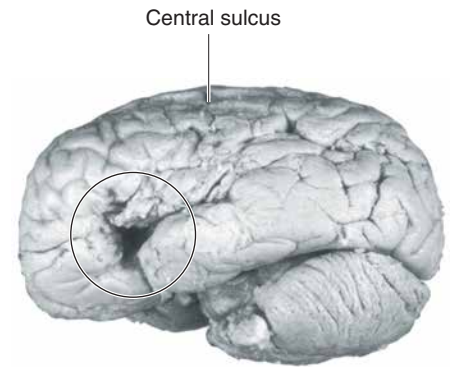
of the exposed surface of the brain of a dog could elicit discrete movements. Scottish neurologist David Ferrier repeated these experiments with monkeys. In 1881, he showed that removal of this same region of the cerebrum causes paralysis of the muscles. Similarly, German physiologist Hermann Munk using experimental ablation found evidence that the occipital lobe of the cerebrum was specifically required for vision.

As you will see in Part II of this book, we now know that there is a very clear division of labor in the cerebrum, with different parts performing very different functions. Today's maps of the functional divisions of the cerebrum rival even the most elaborate of those produced by the phrenologists. The big difference is that unlike the phrenologists, scientists today require solid experimental evidence before attributing a specific function to a portion of the brain. All the same, Gall seems to have had in part the right general idea. It is natural to wonder why Flourens, the pioneer of brain localization of function, was misled into believing that the cerebrum acted as a whole and could not be subdivided. This gifted experimentalist may have missed cerebral localization for many different reasons, but it seems clear that one reason was his visceral disdain for Gall and phrenology. He could not bring himself to agree even remotely with Gall, whom he viewed as a lunatic. This reminds us that science, for better or worse, was and still is subject to both the strengths and the weaknesses of human nature.

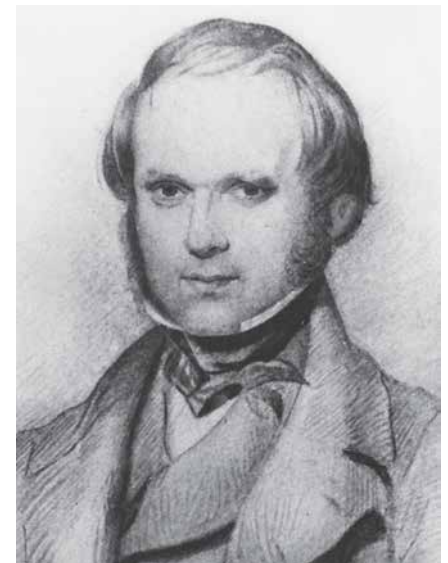
The Evolution of Nervous Systems. In 1859, English biologist Charles Darwin (Figure 1.13) published *On the Origin of Species*. This landmark work articulates a theory of evolution: that species of organisms evolved from a common ancestor. According to his theory, differences among species arise by a process Darwin called *natural selection*. As a result of the mechanisms of reproduction, the physical traits of the offspring are sometimes different from those of the parents. If such traits hold an advantage for survival, the offspring themselves will be more likely to survive to reproduce, thus increasing the likelihood that the advantageous traits are passed on to the next generation. Over the course of many generations, this process led to the development of traits that distinguish species today: flippers on harbor seals, paws on dogs, hands on raccoons, and so on. This single insight revolutionized biology. Today, scientific evidence in many fields ranging from anthropology to molecular genetics overwhelmingly supports the theory of evolution by natural selection.

Darwin included behavior among the heritable traits that could evolve. For example, he observed that many mammalian species show the same reaction when frightened: The pupils of the eyes get bigger, the heart races, hairs stand on end. This is as true for a human as it is for a dog. To Darwin, the similarities of this response pattern indicated that these different species evolved from a common ancestor that possessed the same behavioral trait, which was advantageous presumably because it facilitated escape from predators. Because behavior reflects the activity of the nervous system, we can infer that the brain mechanisms that underlie this fear reaction may be similar, if not identical, across these species.

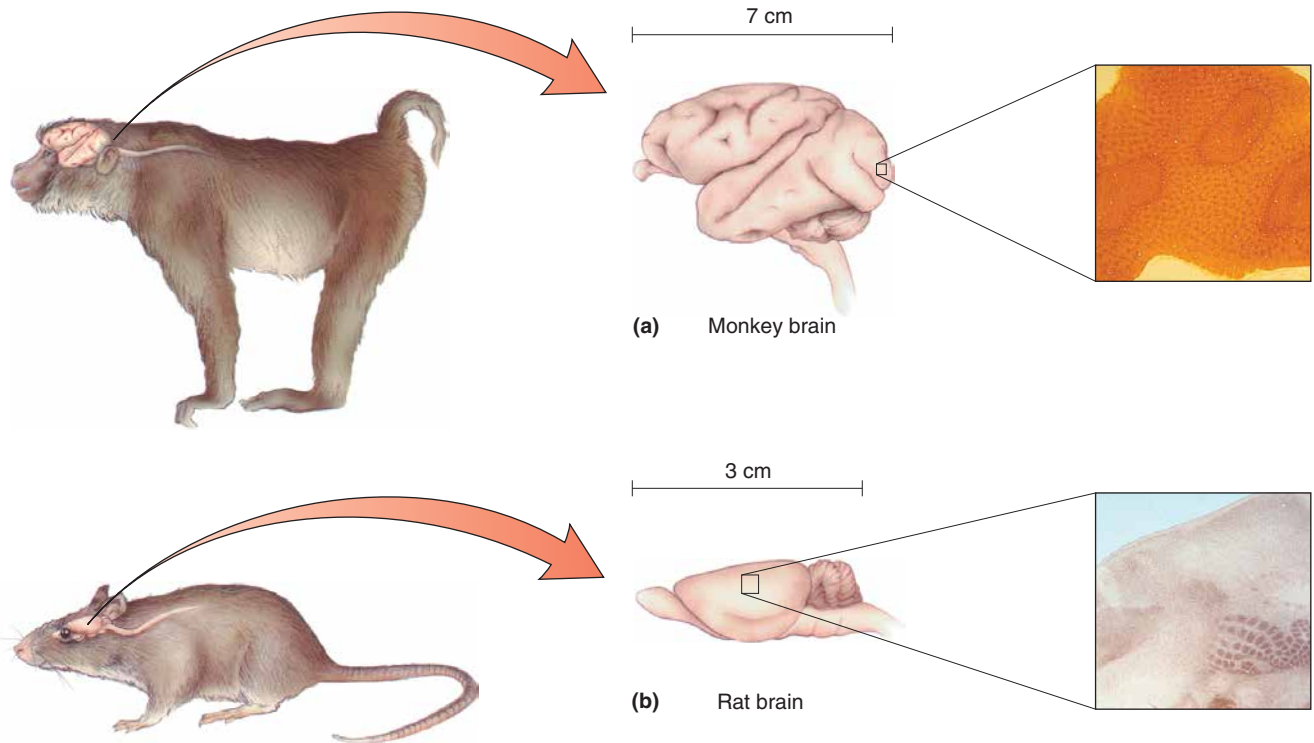
The idea that the nervous systems of different species evolved from common ancestors and may have common mechanisms is the rationale for relating the results of animal experiments to humans. For example, many of the details of electrical impulse conduction along nerve fibers were discovered first in the squid but are now known to apply equally well to humans. Most neuroscientists today use *animal models* to examine processes they wish to understand in humans. For example, rats show clear signs of addiction if they are repeatedly given the chance to



▲ **FIGURE 1.12**
The brain that convinced Broca of localization of function in the cerebrum. This is the preserved brain of a patient who had lost the ability to speak before he died in 1861. The lesion that produced this deficit is circled. (Source: Corsi, 1991, Fig. III, 4.)



▲ **FIGURE 1.13**
Charles Darwin (1809–1882). Darwin proposed his theory of evolution, explaining how species evolve through the process of natural selection. (Source: The Bettman Archive.)



▲ **FIGURE 1.14**

Different brain specializations in monkeys and rats. (a) The brain of the macaque monkey has a highly evolved sense of sight. The boxed region receives information from the eyes. When this region is sliced open and stained to show metabolically active tissue, a mosaic of “blobs” appears. The neurons within the blobs are specialized to analyze colors in the visual world. (b) The brain of a rat has a highly evolved sense of touch to the face. The boxed region receives information from the whiskers. When this region is sliced open and stained to show the location of the neurons, a mosaic of “barrels” appears. Each barrel is specialized to receive input from a single whisker on the rat’s face. (Photomicrographs courtesy of Dr. S.H.C. Hendry.)

self-administer cocaine. Consequently, rats provide a valuable animal model for research focused on understanding how psychoactive drugs exert their effects on the nervous system.

On the other hand, many behavioral traits are highly specialized for the environment (or niche) a species normally occupies. For example, monkeys swinging from branch to branch have a keen sense of sight, while rats slinking through underground tunnels have poor vision but a highly evolved sense of touch using their snout whiskers. Adaptations are reflected in the structure and function of the brain of every species. By comparing the specializations of the brains of different species, neuroscientists have been able to identify which parts of the brain are specialized for different behavioral functions. Examples for monkeys and rats are shown in Figure 1.14.

The Neuron: The Basic Functional Unit of the Brain. Technical advances in microscopy during the early 1800s gave scientists their first opportunity to examine animal tissues at high magnifications. In 1839, German zoologist Theodor Schwann proposed what came to be known as the *cell theory*: All tissues are composed of microscopic units called *cells*.

Although cells in the brain had been identified and described, there was still controversy at that time about whether the individual “nerve

cell” was actually the basic unit of brain function. Nerve cells usually have a number of thin projections, or processes, that extend from a central cell body (Figure 1.15). Initially, scientists could not decide whether the processes from different cells fuse together as do blood vessels in the circulatory system. If this were true, then the “nerve net” of connected nerve cells would represent the elementary unit of brain function.

Chapter 2 presents a brief history of how this issue was resolved. Suffice it to say that by 1900, the individual nerve cell, now called the *neuron*, was recognized to be the basic functional unit of the nervous system.

NEUROSCIENCE TODAY

The history of modern neuroscience is still being written, and the accomplishments to date form the basis for this textbook. We will discuss the most recent developments in the coming chapters. Before we do, let’s take a look at how brain research is conducted today and why it is so important to society.

Levels of Analysis

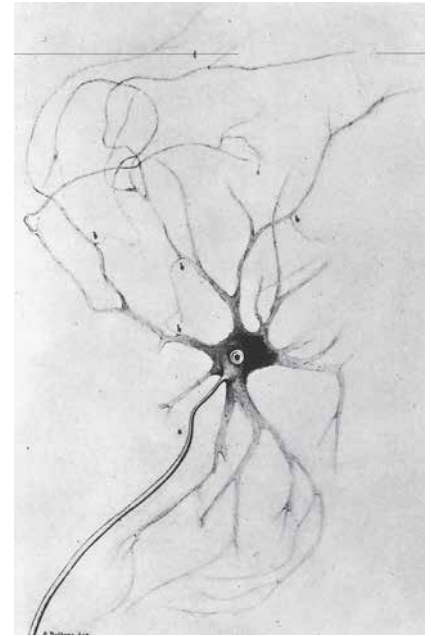
History has clearly shown that understanding how the brain works is a big challenge. To reduce the complexity of the problem, neuroscientists break it into smaller pieces for systematic experimental analysis. This is called the *reductionist approach*. The size of the unit of study defines what is often called the *level of analysis*. In ascending order of complexity, these levels are molecular, cellular, systems, behavioral, and cognitive.

Molecular Neuroscience. The brain has been called the most complex piece of matter in the universe. Brain matter consists of a fantastic variety of molecules, many of which are unique to the nervous system. These different molecules play many different roles that are crucial for brain function: messengers that allow neurons to communicate with one another, sentries that control what materials can enter or leave neurons, conductors that orchestrate neuron growth, archivists of past experiences. The study of the brain at this most elementary level is called *molecular neuroscience*.

Cellular Neuroscience. The next level of analysis is cellular neuroscience, which focuses on studying how all those molecules work together to give neurons their special properties. Among the questions asked at this level are: How many different types of neurons are there, and how do they differ in function? How do neurons influence other neurons? How do neurons become “wired together” during fetal development? How do neurons perform computations?

Systems Neuroscience. Constellations of neurons form complex circuits that perform a common function, such as vision or voluntary movement. Thus, we can speak of the “visual system” and the “motor system,” each of which has its own distinct circuitry within the brain. At this level of analysis, called *systems neuroscience*, neuroscientists study how different neural circuits analyze sensory information, form perceptions of the external world, make decisions, and execute movements.

Behavioral Neuroscience. How do neural systems work together to produce integrated behaviors? For example, are different forms of memory accounted for by different systems? Where in the brain do “mind-altering” drugs act, and what is the normal contribution of these systems to the



▲ **FIGURE 1.15**
An early depiction of a nerve cell.
 Published in 1865, this drawing by German anatomist Otto Deiters shows a nerve cell, or neuron, and its many projections, called *neurites*. For a time it was thought that the neurites from different neurons might fuse together like the blood vessels of the circulatory system. We now know that neurons are distinct entities that communicate using chemical and electrical signals. (Source: Clarke and O'Malley, 1968, Fig. 16.)

regulation of mood and behavior? What neural systems account for gender-specific behaviors? Where are dreams created and what do they reveal? These questions are studied in behavioral neuroscience.

Cognitive Neuroscience. Perhaps the greatest challenge of neuroscience is understanding the neural mechanisms responsible for the higher levels of human mental activity, such as self-awareness, imagination, and language. Research at this level, called *cognitive neuroscience*, studies how the activity of the brain creates the mind.

Neuroscientists

“Neuroscientist” sounds impressive, kind of like “rocket scientist.” But we were all students once, just like you. For whatever reason—maybe we wanted to know why our eyesight was poor, or why a family member suffered a loss of speech after a stroke—we came to share a thirst for knowledge of how the brain works. Perhaps you will, too.

Being a neuroscientist is rewarding, but it does not come easily. Many years of training are required. One may begin by helping out in a research lab during or after college and then going to graduate school to earn a Ph.D. or an M.D. (or both). Several years of post-doctoral training usually follow, learning new techniques or ways of thinking under the direction of an established neuroscientist. Finally, the “young” neuroscientist is ready to set up shop at a university, institute, or hospital.

Broadly speaking, neuroscience research (and neuroscientists) may be divided into three types: *clinical*, *experimental*, and *theoretical*. Clinical research is mainly conducted by physicians (M.D.s). The main medical specialties associated with the human nervous system are neurology, psychiatry, neurosurgery, and neuropathology (Table 1.1). Many who conduct clinical research continue in the tradition of Broca, attempting to deduce from the behavioral effects of brain damage the functions of various parts of the brain. Others conduct studies to assess the benefits and risks of new types of treatment.

Despite the obvious value of clinical research, the foundation for all medical treatments of the nervous system continues to be laid by experimental neuroscientists, who may hold either an M.D. or a Ph.D. The experimental approaches to studying the brain are so broad that they include almost every conceivable methodology. Neuroscience is highly interdisciplinary; however, expertise in a particular methodology may distinguish one neuroscientist from another. Thus, there are *neuroanatomists*, who use sophisticated microscopes to trace connections in the brain; *neurophysiologists*, who use electrodes to measure the brain’s electrical activity; *neuropharmacologists*, who use drugs to study the chemistry of

TABLE 1.1 **Medical Specialists Associated with the Nervous System**

Specialist	Description
Neurologist	An M.D. trained to diagnose and treat diseases of the nervous system
Psychiatrist	An M.D. trained to diagnose and treat disorders of mood and behavior
Neurosurgeon	An M.D. trained to perform surgery on the brain and spinal cord
Neuropathologist	An M.D. or Ph.D. trained to recognize the changes in nervous tissue that result from disease

TABLE 1.2 Types of Experimental Neuroscientists

Type	Description
Developmental neurobiologist	Analyzes the development and maturation of the brain
Molecular neurobiologist	Uses the genetic material of neurons to understand the structure and function of brain molecules
Neuroanatomist	Studies the structure of the nervous system
Neurochemist	Studies the chemistry of the nervous system
Neuroethologist	Studies the neural basis of species-specific animal behaviors in natural settings
Neuropharmacologist	Examines the effects of drugs on the nervous system
Neurophysiologist	Measures the electrical activity of the nervous system
Physiological psychologist (biological psychologist, psychobiologist)	Studies the biological basis of behavior
Psychophysicist	Quantitatively measures perceptual abilities

brain function; *molecular neurobiologists*, who probe the genetic material of neurons to find clues about the structure of brain molecules; and so on. Table 1.2 lists some of the types of experimental neuroscientists.

Theoretical neuroscience is a relatively young discipline, in which researchers use mathematical and computational tools to understand the brain at all levels of analysis. In the tradition of physics, theoretical neuroscientists attempt to make sense of the vast amounts of data generated by experimentalists, with the goals of helping focus experiments on questions of greatest importance and establishing the mathematical principles of nervous system organization.

The Scientific Process

Neuroscientists of all stripes endeavor to establish truths about the nervous system. Regardless of the level of analysis they choose, they work according to a scientific process consisting of four essential steps: observation, replication, interpretation, and verification.

Observation. Observations are typically made during experiments designed to test a particular hypothesis. For example, Bell hypothesized that the ventral roots contain the nerve fibers that control the muscles. To test this idea, he performed an experiment in which he cut these fibers and then observed whether or not muscular paralysis resulted. Other types of observation derive from carefully watching the world around us, or from introspection, or from human clinical cases. For example, Broca's careful observations led him to correlate left frontal lobe damage with the loss of the ability to speak.

Replication. Any observation, whether experimental or clinical, must be replicated. Replication simply means repeating the experiment on different subjects or making similar observations in different patients, as many times as necessary to rule out the possibility that the observation occurred by chance.

Interpretation. Once the scientist believes the observation is correct, he or she interprets it. Interpretations depend on the state of knowledge (or ignorance) at the time and on the scientist's preconceived notions

(or “mind set”). Interpretations therefore do not always withstand the test of time. For example, at the time he made his observations, Flourens was unaware that the cerebrum of a bird is fundamentally different from that of a mammal. Thus, he wrongly concluded from experimental ablations in birds that there was no localization of certain functions in the cerebrum of mammals. Moreover, as mentioned before, his profound distaste for Gall surely also colored his interpretation. The point is that the correct interpretation often is not made until long after the original observations. Indeed, major breakthroughs sometimes occur when old observations are reinterpreted in a new light.

Verification. The final step of the scientific process is verification. This step is distinct from the replication the original observer performed. Verification means that the observation is sufficiently robust that any competent scientist who precisely follows the protocols of the original observer can reproduce it. Successful verification generally means that the observation is accepted as fact. However, not all observations can be verified, sometimes because of inaccuracies in the original report or insufficient replication. But failure to verify usually stems from the fact that unrecognized variables, such as temperature or time of day, contributed to the original result. Thus, the process of verification, if affirmative, establishes new scientific fact, or, if negative, suggests new interpretations for the original observation.

Occasionally, one reads in the popular press about a case of scientific fraud. Researchers face keen competition for limited research funds and feel considerable pressure to “publish or perish.” In the interest of expediency, a few have actually published “observations” they in fact never made. Fortunately, such instances of fraud are rare, thanks to the scientific process. Before long, other scientists find they are unable to verify the fraudulent observations and question how they could have been made in the first place. The fact that we can fill this book with so much knowledge about the nervous system stands as a testament to the value of the scientific process.

The Use of Animals in Neuroscience Research

Most of what we know about the nervous system has come from experiments on animals. In most cases, the animals are killed so their brains can be examined neuroanatomically, neurophysiologically, and/or neurochemically. The fact that animals are sacrificed for the pursuit of human knowledge raises questions about the ethics of animal research.

The Animals. Let’s begin by putting the issue in perspective. Throughout history, humans have considered animals and animal products as renewable natural resources that can be used for food, clothing, transportation, recreation, sport, and companionship. The animals used in research, education, and testing have always been a small fraction of those used for other purposes. For example, in the United States, the number of animals used in all types of biomedical research is very small compared to the number killed for food. The number used specifically in neuroscience research is much smaller still.

Neuroscience experiments are conducted using many different species, ranging from snails to monkeys. The choice of species is generally dictated by the question under investigation, the level of analysis, and the extent to which the knowledge gained can be related to humans. As a rule, the more basic the process under investigation, the more distant can

be the evolutionary relationship with humans. Thus, experiments aimed at understanding the molecular basis of nerve impulse conduction can be carried out with a distantly related species, such as the squid. On the other hand, understanding the neural basis of movement and perceptual disorders in humans has required experiments with more closely related species, such as the macaque monkey. Today, more than half of the animals used for neuroscience research are rodents—mice and rats—that are bred specifically for this purpose.

Animal Welfare. In the developed world today, most educated adults have a concern for animal welfare. Neuroscientists share this concern and work to ensure that animals are well treated. Society has not always placed such value on animal welfare, however, as reflected in some of the scientific practices of the past. For example, in his experiments early in the nineteenth century, Magendie used unanesthetized puppies (for which he was later criticized by his scientific rival Bell). Fortunately, heightened awareness of animal welfare has more recently led to significant improvements in how animals are treated in biomedical research.

Today, neuroscientists accept certain moral responsibilities toward their animal subjects:

1. Animals are used only in worthwhile experiments that promise to advance our knowledge of the nervous system.
2. All necessary steps are taken to minimize pain and distress experienced by the experimental animals (use of anesthetics, analgesics, etc.).
3. All possible alternatives to the use of animals are considered.

Adherence to this ethical code is monitored in a number of ways. First, research proposals must pass a review by the Institutional Animal Care and Use Committee (IACUC), as mandated by U.S. federal law. Members of this committee include a veterinarian, scientists in other disciplines, and nonscientist community representatives. After passing the IACUC review, proposals are evaluated for scientific merit by a panel of expert neuroscientists. This step ensures that only the most worthwhile projects are carried out. Then, when neuroscientists submit their observations for publication in the professional journals, the papers are carefully reviewed by other neuroscientists for both scientific merit and animal welfare concerns. Reservations about either issue can lead to rejection of the paper, which in turn can lead to a loss of funding for the research. In addition to these monitoring procedures, federal law sets strict standards for the housing and care of laboratory animals.

Animal Rights. Most people accept the necessity for animal experimentation to advance knowledge, as long as it is performed humanely and with the proper respect for animals' welfare. However, a vocal and increasingly violent minority seeks the total abolition of animal use for human purposes, including experimentation. These people subscribe to a philosophical position often called *animal rights*. According to this way of thinking, animals have the same legal and moral rights as humans.

If you are an animal lover, you may be sympathetic to this position. But consider the following questions. Are you willing to deprive yourself and your family of medical procedures that were developed using animals? Is the death of a mouse equivalent to the death of a human being? Is keeping a pet the moral equivalent of slavery? Is eating meat the moral equivalent of murder? Is it unethical to take the life of a pig to save the life of a child? Is controlling the rodent population in the sewers or the roach population in your home morally equivalent to the Holocaust?

If your answer is no to any of these questions, then you do not subscribe to the philosophy of animal rights. *Animal welfare*—a concern that all responsible people share—must not be confused with animal rights.

Animal rights activists have vigorously pursued their agenda against animal research, sometimes with alarming success. They have manipulated public opinion with repeated allegations of cruelty in animal experiments that are grossly distorted or blatantly false. They have vandalized laboratories, destroying years of hard-won scientific data and hundreds of thousands of dollars of equipment (that you, the taxpayer, had paid for). With threats of violence they have driven some researchers out of science altogether.

Fortunately, the tide is turning. Thanks to the efforts of a number of people, scientists and nonscientists alike, the false claims of the extremists have been exposed, and the benefits to humankind of animal research have been extolled (Figure 1.16). Considering the staggering toll in terms of human suffering that results from disorders of the nervous system, neuroscientists take the position that it is our responsibility to wisely use all the resources nature has provided, including animals, to gain an understanding of how the brain functions in health and in disease.

It's the animals you don't see
that really helped her recover.



Recently, a surgical technique perfected on animals was used to remove a malignant tumor from a little girl's brain. We lost some lab animals. But look what we saved.

▲ **FIGURE 1.16**

Our debt to animal research. This poster counters the claims of animal rights activists by raising public awareness of the benefits of animal research. (Source: Foundation for Biomedical Research.)

TABLE 1.3 Some Major Disorders of the Nervous System

Disorder	Description
Alzheimer's disease	A progressive degenerative disease of the brain, characterized by dementia and always fatal
Autism	A disorder emerging in early childhood characterized by impairments in communication and social interactions, and restricted and repetitive behaviors
Cerebral palsy	A motor disorder caused by damage to the cerebrum before, during, or soon after birth
Depression	A serious disorder of mood, characterized by insomnia, loss of appetite, and feelings of dejection
Epilepsy	A condition characterized by periodic disturbances of brain electrical activity that can lead to seizures, loss of consciousness, and sensory disturbances
Multiple sclerosis	A progressive disease that affects nerve conduction, characterized by episodes of weakness, lack of coordination, and speech disturbance
Parkinson's disease	A progressive disease of the brain that leads to difficulty in initiating voluntary movement
Schizophrenia	A severe psychotic illness characterized by delusions, hallucinations, and bizarre behavior
Spinal paralysis	A loss of feeling and movement caused by traumatic damage to the spinal cord
Stroke	A loss of brain function caused by disruption of the blood supply, usually leading to permanent sensory, motor, or cognitive deficit

The Cost of Ignorance: Nervous System Disorders

Modern neuroscience research is expensive, but the cost of ignorance about the brain is far greater. Table 1.3 lists some of the disorders that affect the nervous system. It is likely that your family has felt the impact of one or more of these. Let's look at a few brain disorders and examine their effects on society.

Alzheimer's disease and Parkinson's disease are both characterized by progressive degeneration of specific neurons in the brain. Parkinson's disease, which results in a crippling impairment of voluntary movement, currently affects over 500,000 Americans.¹ Alzheimer's disease leads to dementia, a state of confusion characterized by the loss of ability to learn new information and to recall previously acquired knowledge. Dementia affects an estimated 18% of people over age 85.² The number of Americans with dementia totals well over 4 million. Indeed, dementia is now recognized as not an inevitable outcome of aging, as was once believed, but as a sign of brain disease. Alzheimer's disease progresses mercilessly, robbing its victims first of their mind, then of control over basic bodily functions, and finally of their life; the disease is always fatal. In the United States, the annual cost of care for people with dementia is greater than \$100 billion and rising at an alarming rate.

Depression and schizophrenia are disorders of mood and thought. Depression is characterized by overwhelming feelings of dejection,

¹National Institute of Neurological Disorders and Stroke. "Parkinson Disease Background." October 18, 2004.

²U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality. "Approximately 5 Percent of Seniors Report One or More Cognitive Disorders." March 2011.

worthlessness, and guilt. Over 30 million Americans will experience a major depressive illness at some time in their lives. Depression is the leading cause of suicide, which claims more than 30,000 lives each year in the United States.³

Schizophrenia is a severe psychiatric disorder characterized by delusions, hallucinations, and bizarre behavior. This disease often strikes at the prime of life—adolescence or early adulthood—and can persist for life. Over 2 million Americans suffer from schizophrenia. The National Institute of Mental Health (NIMH) estimates that mental disorders, such as depression and schizophrenia, cost the United States in excess of \$150 billion annually.

Stroke is the fourth leading cause of death in the United States. Stroke victims who do not die, over half a million every year, are likely to be permanently disabled. The annual cost of stroke nationwide is \$54 billion.⁴

Alcohol or drug addiction affects virtually every family in the United States. The cost in terms of treatment, lost wages, and other consequences exceeds \$600 billion per year.⁵

These few examples only scratch the surface. *More Americans are hospitalized with neurological and mental disorders than with any other major disease group, including heart disease and cancer.*

The economic costs of brain dysfunction are enormous, but they pale in comparison with the staggering emotional toll on victims and their families. The prevention and treatment of brain disorders require an understanding of normal brain function, and this basic understanding is the goal of neuroscience. Neuroscience research has already contributed to the development of increasingly effective treatments for Parkinson's disease, depression, and schizophrenia. New strategies are being tested to rescue dying neurons in people with Alzheimer's disease and those who have had a stroke. Major progress has been made in our understanding of how drugs and alcohol affect the brain and how they lead to addictive behavior. The material in this book demonstrates that a lot is known about the function of the brain. But what we know is insignificant compared with what is still left to be learned.

CONCLUDING REMARKS

The historical foundations of neuroscience were established by many people over many generations. Men and women today are working at all levels of analysis, using all types of technology, to shed more light on the functions of the brain. The fruits of this labor form the basis for this textbook.

The goal of neuroscience is to understand how nervous systems function. Many important insights can be gained from a vantage point outside the head. Because the brain's activity is reflected in behavior, careful behavioral measurements inform us of the capabilities and limitations of brain function. Computer models that reproduce the brain's computational properties can help us understand how these properties might arise. From the scalp, we can measure brain waves, which tell us something about the electrical activity of different parts of the brain during

³National Institute of Mental Health. "Suicide in the U.S.: Statistics and Prevention." September 27, 2010.

⁴American Heart Association/American Stroke Association. "Impact of Stroke (Stroke Statistics)." May 1, 2012.

⁵National Institutes of Health, National Institute of Drug Abuse. "DrugFacts: Understanding Drug Abuse and Addiction." March 2011.

various behavioral states. New computer-assisted imaging techniques enable researchers to examine the structure of the living brain as it sits in the head. And using even more sophisticated imaging methods, we are beginning to see which different parts of the human brain become active under different conditions. But none of these noninvasive methods, old or new, can fully substitute for experimentation with living brain tissue. We cannot make sense of remotely detected signals without being able to see how they are generated and what their significance is. To understand *how* the brain works, we must open the head and examine what's inside—neuroanatomically, neurophysiologically, and neurochemically.

The pace of neuroscience research today is truly breathtaking, raising hopes that soon we will have new treatments for the wide range of nervous system disorders that debilitate and cripple millions of people annually. However, despite the progress in recent decades and the centuries preceding them, we still have a long way to go before we fully understand how the brain performs all of its amazing feats. But this is the fun of being a neuroscientist: Because our ignorance of brain function is so vast, a startling new discovery lurks around virtually every corner.



REVIEW QUESTIONS

1. What are brain ventricles, and what functions have been ascribed to them over the ages?
2. What experiment did Bell perform to show that the nerves of the body contain a mixture of sensory and motor fibers?
3. What did Flourens' experiments suggest were the functions of the cerebrum and the cerebellum?
4. What is the meaning of the term *animal model*?
5. A region of the cerebrum is now called Broca's area. What function do you think this region performs, and why?
6. What are the different levels of analysis in neuroscience research? What questions do researchers ask at each level?
7. What are the steps in the scientific process? Describe each one.



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CHAPTER TWO

Neurons and Glia

INTRODUCTION

THE NEURON DOCTRINE

The Golgi Stain

Cajal's Contribution

BOX 2.1 OF SPECIAL INTEREST: *Advances in Microscopy*

THE PROTOTYPICAL NEURON

The Soma

The Nucleus

Neuronal Genes, Genetic Variation, and Genetic Engineering

BOX 2.2 BRAIN FOOD: *Expressing One's Mind in the Post-Genomic Era*

BOX 2.3 PATH OF DISCOVERY: *Gene Targeting in Mice, by Mario Capecchi*

Rough Endoplasmic Reticulum

Smooth Endoplasmic Reticulum and the Golgi Apparatus

The Mitochondrion

The Neuronal Membrane

The Cytoskeleton

Microtubules

BOX 2.4 OF SPECIAL INTEREST: *Alzheimer's Disease and the Neuronal*

Cytoskeleton

Microfilaments

Neurofilaments

The Axon

The Axon Terminal

The Synapse

Axoplasmic Transport

BOX 2.5 OF SPECIAL INTEREST: *Hitching a Ride with Retrograde Transport*

Dendrites

BOX 2.6 OF SPECIAL INTEREST: *Intellectual Disability and Dendritic Spines*

CLASSIFYING NEURONS

Classification Based on Neuronal Structure

Number of Neurites

Dendrites

Connections

Axon Length

Classification Based on Gene Expression

BOX 2.7 BRAIN FOOD: *Understanding Neuronal Structure and Function with Incredible Cre*

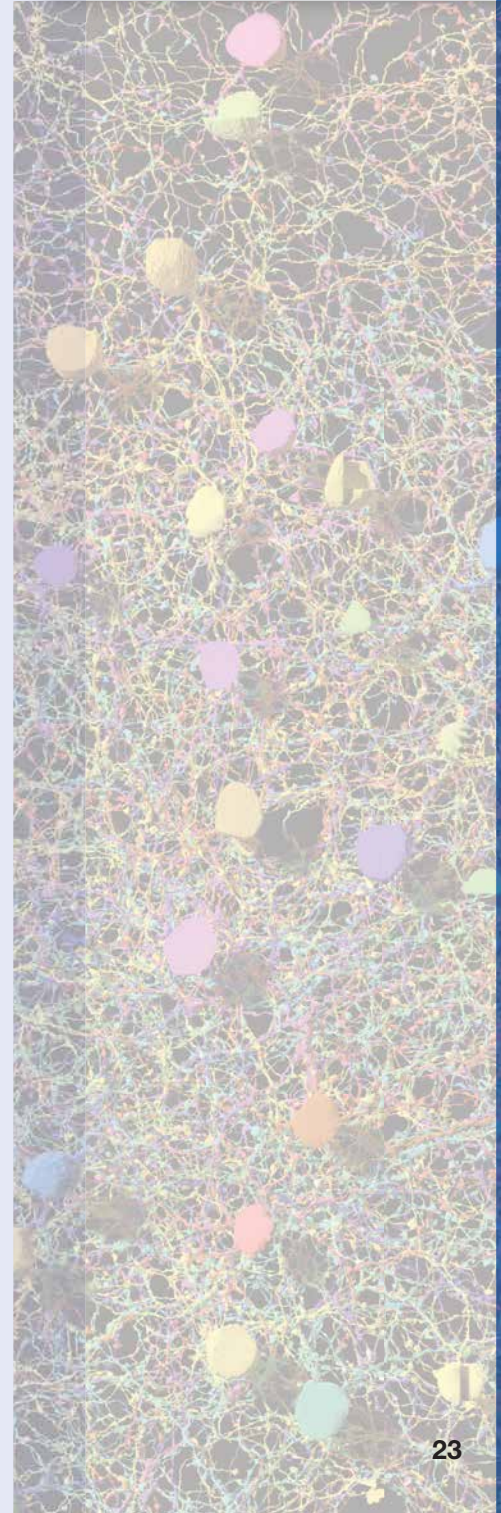
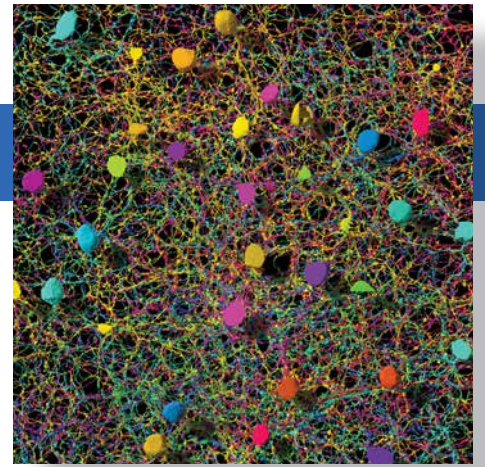
GLIA

Astrocytes

Myelinating Glia

Other Non-Neuronal Cells

CONCLUDING REMARKS



INTRODUCTION

All tissues and organs in the body consist of cells. The specialized functions of cells and how they interact determine the functions of organs. The brain is an organ—to be sure, the most sophisticated and complex organ that nature has devised. But the basic strategy for unraveling its functions is no different from that used to investigate the pancreas or the lung. We must begin by learning how brain cells work individually and then see how they are assembled to work together. In neuroscience, there is no need to separate *mind* from *brain*; once we fully understand the individual and concerted actions of brain cells, we will understand our mental abilities. The organization of this book reflects this “neurophilosophy.” We start with the cells of the nervous system—their structure, function, and means of communication. In later chapters, we will explore how these cells are assembled into circuits that mediate sensation, perception, movement, speech, and emotion.

This chapter focuses on the structure of the different types of cells in the nervous system: *neurons* and *glia*. These are broad categories, within which are many types of cells that differ in structure, chemistry, and function. Nonetheless, the distinction between neurons and glia is important. Although there are approximately equal numbers of neurons and glia in the adult human brain (roughly 85 billion of each type), neurons are responsible for most of the unique functions of the brain. It is the **neurons** that sense changes in the environment, communicate these changes to other neurons, and command the body’s responses to these sensations. **Glia**, or **glial cells**, contribute to brain function mainly by insulating, supporting, and nourishing neighboring neurons. If the brain were a chocolate chip cookie and the neurons were chocolate chips, the glia would be the cookie dough that fills all the other space and suspends the chips in their appropriate locations. Indeed, the term *glia* is derived from the Greek word for “glue,” giving the impression that the main function of these cells is to keep the brain from running out of our ears! Although this simple view belies the importance of glial function, as we shall see later in this chapter, we are confident that neurons perform most information processing in the brain, so neurons receive most of our attention.

Neuroscience, like other fields, has a language all its own. To use this language, you must learn the vocabulary. After you have read this chapter, take a few minutes to review the key terms list and make sure you understand the meaning of each term. Your neuroscience vocabulary will grow as you work your way through the book.

THE NEURON DOCTRINE

To study the structure of brain cells, scientists have had to overcome several obstacles. The first was the small size. Most cells are in the range of 0.01–0.05 mm in diameter. The tip of an unsharpened pencil lead is about 2 mm across; neurons are 40–200 times smaller. (For a review of the metric system, see Table 2.1.) Because neurons cannot be seen by the naked eye, cellular neuroscience could not progress before the development of the compound microscope in the late seventeenth century. Even then, obstacles remained. To observe brain tissue using a microscope, it was necessary to make very thin slices, ideally not much thicker than the diameter of the cells. However, brain tissue has a consistency like a bowl of Jell-O: not firm enough to make thin slices. Thus,

TABLE 2.1 Units of Size in the Metric System

Unit	Abbreviation	Meter Equivalent	Real-World Equivalent
Kilometer	km	10^3 m	About two-thirds of a mile
Meter	m	1 m	About 3 feet
Centimeter	cm	10^{-2} m	Thickness of your little finger
Millimeter	mm	10^{-3} m	Thickness of your toenail
Micrometer	μm	10^{-6} m	Near the limit of resolution for the light microscope
Nanometer	nm	10^{-9} m	Near the limit of resolution for the electron microscope

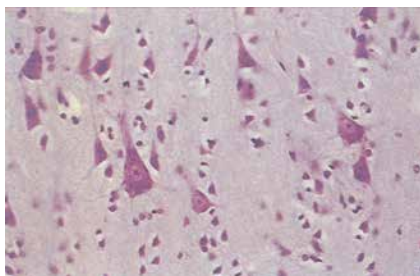
the anatomical study of brain cells had to await a method to harden the tissue without disturbing its structure and an instrument that could produce very thin slices. Early in the nineteenth century, scientists discovered how to harden, or “fix,” tissues by immersing them in formaldehyde, and they developed a special device called a *microtome* to make very thin slices.

These technical advances spawned the field of **histology**, the microscopic study of the structure of tissues. But scientists studying brain structure faced yet another obstacle. Freshly prepared brain tissue has a uniform, cream-colored appearance under the microscope, with no differences in pigmentation to enable histologists to resolve individual cells. The final breakthrough in neurohistology was the introduction of stains that selectively color some, but not all, parts of the cells in brain tissue.

One stain still used today was introduced by the German neurologist Franz Nissl in the late nineteenth century. Nissl showed that a class of basic dyes would stain the nuclei of all cells as well as clumps of material surrounding the nuclei of neurons (Figure 2.1). These clumps are called *Nissl bodies*, and the stain is known as the **Nissl stain**. The Nissl stain is extremely useful for two reasons: It distinguishes between neurons and glia, and it enables histologists to study the arrangement, or **cytoarchitecture**, of neurons in different parts of the brain. (The prefix *cyto-* is from the Greek word for “cell.”) The study of cytoarchitecture led to the realization that the brain consists of many specialized regions. We now know that each region performs a different function.

The Golgi Stain

The Nissl stain, however, could not tell the whole story. A Nissl-stained neuron looks like little more than a lump of protoplasm containing a



◀ **FIGURE 2.1**

Nissl-stained neurons. A thin slice of brain tissue has been stained with cresyl violet, a Nissl stain. The clumps of deeply stained material around the cell nuclei are Nissl bodies. (Source: Hammersen, 1980, Fig. 493.)

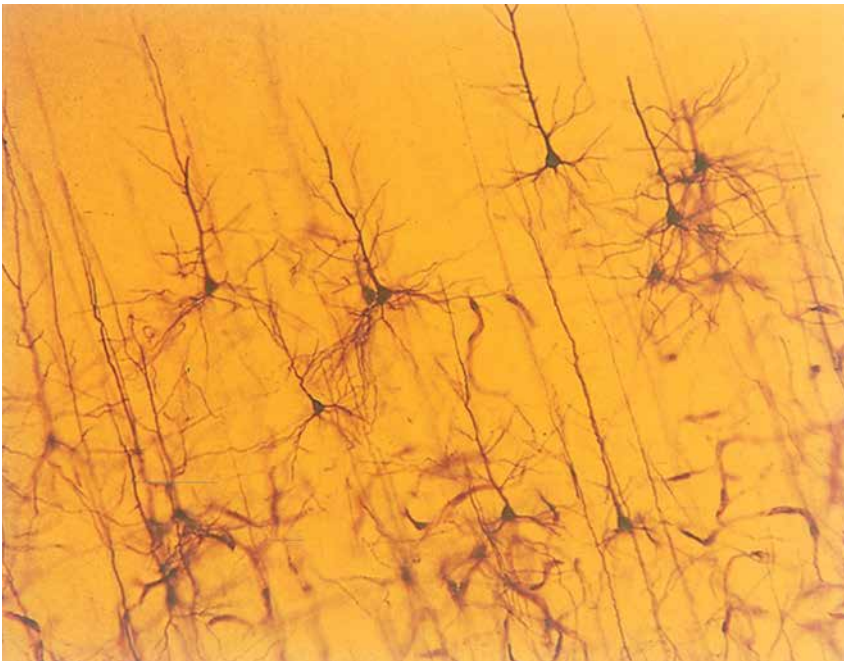


▲ **FIGURE 2.2**
Camillo Golgi (1843–1926).
 (Source: Finger, 1994, Fig. 3.22.)

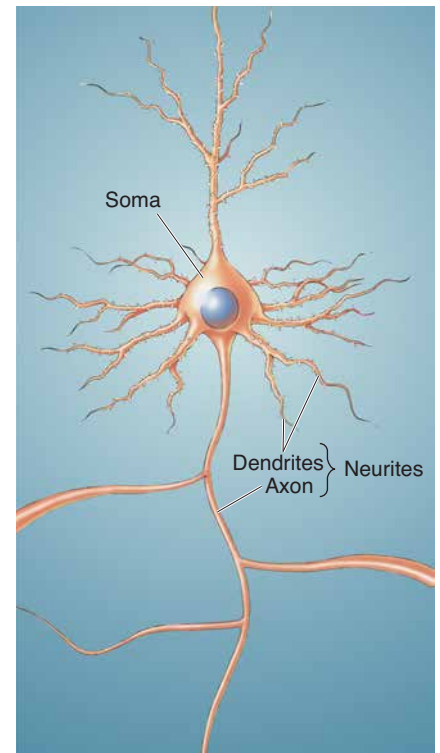
nucleus. Neurons are much more than that, but how much more was not recognized before Italian histologist Camillo Golgi devised a new method (Figure 2.2). In 1873, Golgi discovered that soaking brain tissue in a silver chromate solution, now called the **Golgi stain**, makes a small percentage of neurons become darkly colored in their entirety (Figure 2.3). This revealed that the neuronal cell body, the region of the neuron around the nucleus that is shown with the Nissl stain, is actually only a small fraction of the total structure of the neuron. Notice in Figures 2.1 and 2.3 how different histological stains can provide strikingly different views of the same tissue. Today, neurohistology remains an active field in neuroscience, along with its credo: “The gain in brain is mainly in the stain.”

The Golgi stain shows that neurons have at least two distinguishable parts: a central region that contains the cell nucleus and numerous thin tubes that radiate away from the central region. The swollen region containing the cell nucleus has several names that are used interchangeably: **cell body**, **soma** (plural: somata), and **perikaryon** (plural: perikarya). The thin tubes that radiate from the soma are called **neurites** and are of two types: **axons** and **dendrites** (Figure 2.4).

The cell body usually gives rise to a single axon. The axon is of uniform diameter throughout its length, and any branches from it generally extend at right angles. Because axons can extend over great distances in the body (a meter or more), histologists of the day immediately recognized that axons must act like “wires” that carry the output of the neurons. Dendrites, on the other hand, are rarely longer than 2 mm. Many dendrites extend from the cell body and generally taper to a fine point.



▲ **FIGURE 2.3**
Golgi-stained neurons. (Source: Hubel, 1988, p. 126.)



▲ **FIGURE 2.4**
The basic parts of a neuron.

Early histologists recognized that because dendrites come in contact with many axons, they must act as the antennae of the neuron to receive incoming signals, or input.

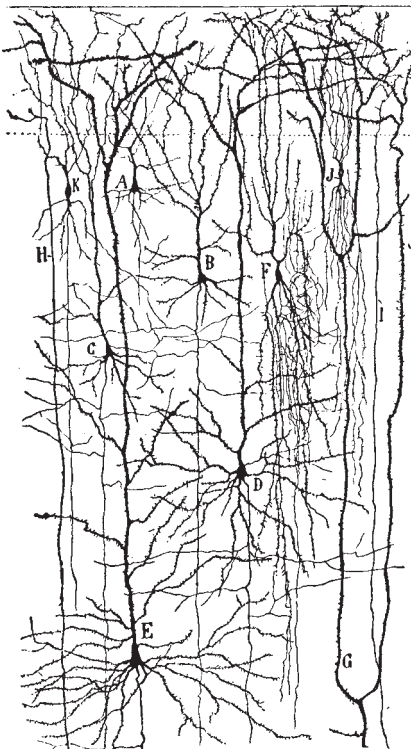
Cajal's Contribution

Golgi invented the stain, but a Spanish contemporary used it to greatest effect. Santiago Ramón y Cajal was a skilled histologist and artist who learned about Golgi's method in 1888 (Figure 2.5). In a remarkable series of publications over the next 25 years, Cajal used the Golgi stain to work out the circuitry of many regions of the brain (Figure 2.6). Curiously, Golgi and Cajal drew completely opposite conclusions about neurons. Golgi championed the view that the neurites of different cells are fused together to form a continuous reticulum, or network, similar to the arteries and veins of the circulatory system. According to this reticular theory, the brain is an exception to the cell theory, which states that the individual cell is the elementary functional unit of all animal tissues. Cajal, on the other hand, argued forcefully that the neurites of different neurons are not continuous with each other and *communicate by contact, not continuity*. This idea that cell theory also applies to neurons came to be known as the **neuron doctrine**. Although Golgi and Cajal shared the Nobel Prize in 1906, they remained rivals to the end.

The scientific evidence over the next 50 years strongly supported the neuron doctrine, but final proof had to wait for the electron microscope in the 1950s (Box 2.1). With the increased resolving power of the electron microscope, it was finally possible to show that the neurites of different neurons are not continuous with one another (Figure 2.7). Thus, our starting point in the exploration of the brain must be the individual neuron.



▲ **FIGURE 2.5**
Santiago Ramón y Cajal (1852–1934).
(Source: Finger, 1994, Fig. 3.26.)



◀ **FIGURE 2.6**
One of Cajal's many drawings of brain circuitry. The letters label the different elements Cajal identified in an area of the human cerebral cortex that controls voluntary movement. We will learn more about this part of the brain in Chapter 14. (Source: DeFelipe and Jones, 1998, Fig. 90.)



BOX 2.1 OF SPECIAL INTEREST

Advances in Microscopy

The human eye can distinguish two points only if they are separated by more than about one-tenth of a millimeter ($100\ \mu\text{m}$). Thus, we can say that $100\ \mu\text{m}$ is near the limit of resolution for the unaided eye. Neurons have a diameter of about $20\ \mu\text{m}$, and neurites can be as small as a fraction of a micrometer. The light microscope, therefore, was a necessary development before neuronal structure could be studied. But this type of microscopy has a theoretical limit imposed by the properties of microscope lenses and visible light. With the standard light microscope, the limit of resolution is about $0.1\ \mu\text{m}$. Because the space between neurons is only $0.02\ \mu\text{m}$ ($20\ \text{nm}$), it's no wonder that two esteemed scientists, Golgi and Cajal, disagreed about whether neurites were continuous from one cell to the next. This question could not be answered until about 70 years ago when the electron microscope was developed and applied to biological specimens.

The electron microscope uses an electron beam instead of light to form images, dramatically increasing the resolving power. The limit of resolution for an electron microscope is about $0.1\ \text{nm}$ —a million times better than the unaided eye and a thousand times better than a light microscope. Our insights into the fine structure of the inside of neurons—the ultrastructure—have all come from electron microscopic examination of the brain.

Today, microscopes on the leading edge of technology use laser beams to illuminate tissue and computers to create digital images (Figure A). Neuroscientists now routinely introduce into neurons molecules that fluoresce when illuminated by laser light. The fluorescence is recorded by

sensitive detectors, and the computer takes these data and reconstructs the image of the neuron. Unlike the traditional methods of light and electron microscopy, which require tissue fixation, these new techniques give neuroscientists the ability to peer into brain tissue that is still alive. Furthermore, they have allowed “super-resolution” imaging, breaking the limits imposed by traditional light microscopy to reveal structures as small as $20\ \text{nm}$ across.

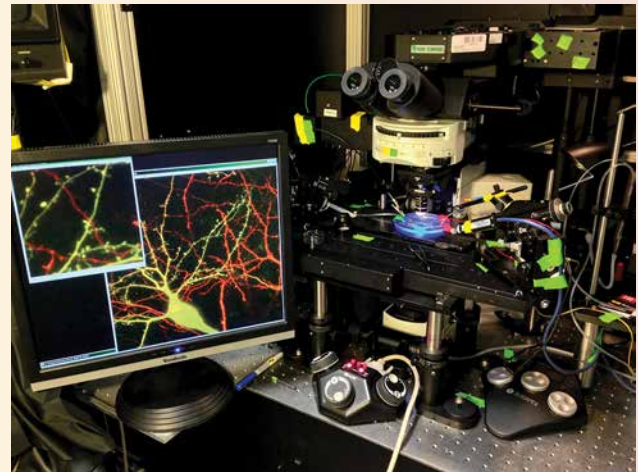


Figure A

A laser microscope and computer display of a fluorescent neuron and dendrites. (Source: Dr. Miquel Bosch, Massachusetts Institute of Technology.)

► FIGURE 2.7

Neurites in contact, not continuity.

These neurites were reconstructed from a series of images made using an electron microscope. The axon (colored yellow) is in contact with a dendrite (colored blue). (Source: Courtesy of Dr. Sebastian Seung, Princeton University, and Kris Krug, Pop Tech.)



THE PROTOTYPICAL NEURON

As we have seen, the neuron (also called a *nerve cell*) consists of several parts: the soma, the dendrites, and the axon. The inside of the neuron is separated from the outside by the *neuronal membrane*, which lies like a circus tent on an intricate internal scaffolding, giving each part of the cell its special three-dimensional appearance. Let's explore the inside of the neuron and learn about the functions of the different parts (Figure 2.8).

The Soma

We begin our tour at the soma, the roughly spherical central part of the neuron. The cell body of the typical neuron is about 20 μm in diameter. The watery fluid inside the cell, called the **cytosol**, is a salty, potassium-rich solution that is separated from the outside by the neuronal membrane. Within the soma are a number of membrane-enclosed structures called **organelles**.

The cell body of the neuron contains the same organelles found in all animal cells. The most important ones are the nucleus, the rough endoplasmic reticulum, the smooth endoplasmic reticulum, the Golgi apparatus, and the mitochondria. Everything contained within the confines of the cell membrane, including the organelles but excluding the nucleus, is referred to collectively as the **cytoplasm**.

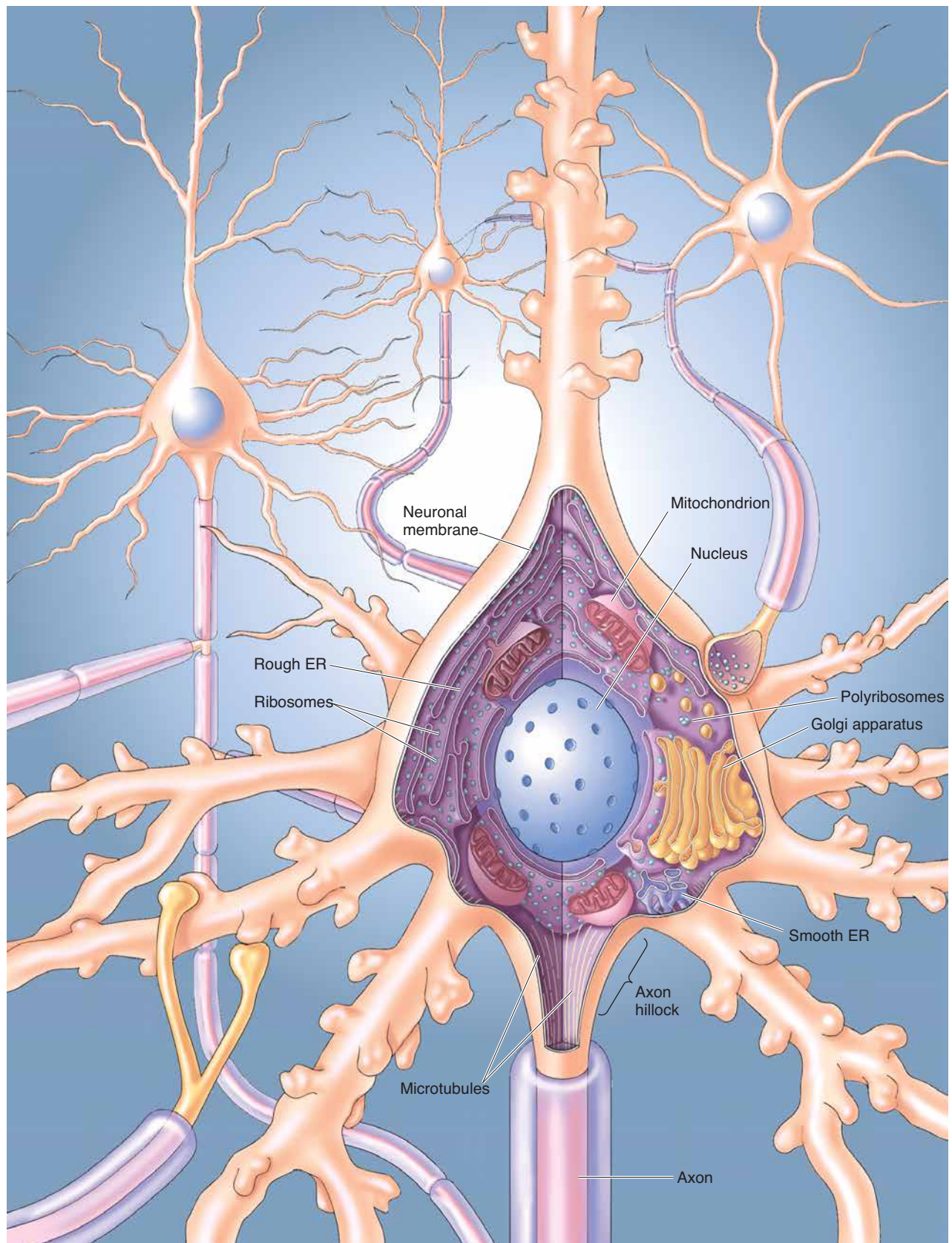
The Nucleus. Its name derived from the Latin word for “nut,” the **nucleus** of the cell is spherical, centrally located, and about 5–10 μm across. It is contained within a double membrane called the *nuclear envelope*. The nuclear envelope is perforated by pores about 0.1 μm across.

Within the nucleus are **chromosomes** which contain the genetic material **DNA (deoxyribonucleic acid)**. Your DNA was passed on to you from your parents and it contains the blueprint for your entire body. The DNA in each of your neurons is the same, and it is the same as the DNA in the cells of your liver and kidney and other organs. What distinguishes a neuron from a liver cell are the specific parts of the DNA that are used to assemble the cell. These segments of DNA are called **genes**.

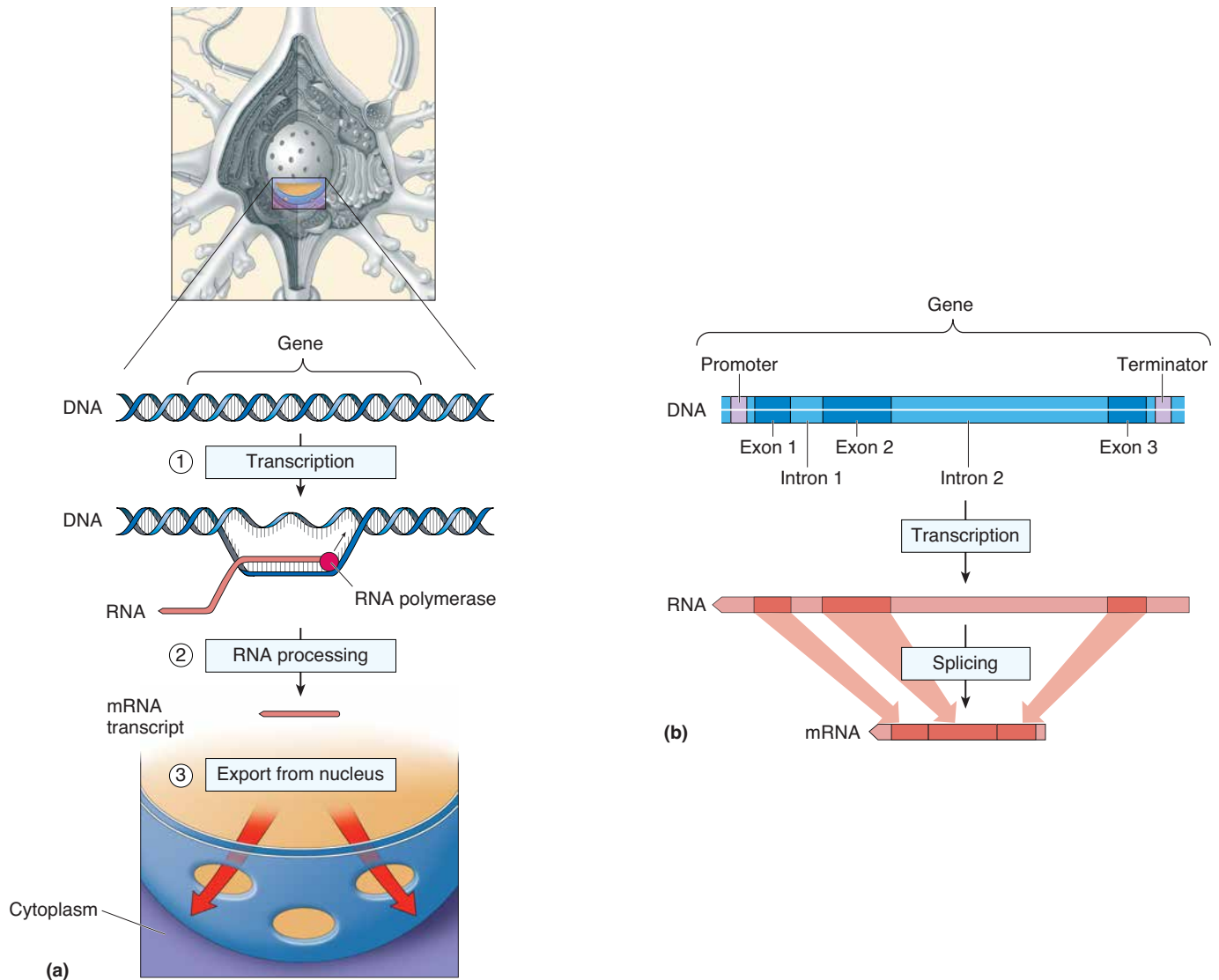
Each chromosome contains an uninterrupted double-strand braid of DNA, 2 nm wide. If the DNA from the 46 human chromosomes were laid out straight, end to end, it would measure more than 2 m in length. If we were to compare this total length of DNA to the total string of letters that make up this book, the genes would be analogous to the individual words. Genes are from 0.1 to several micrometers in length.

The “reading” of the DNA is known as **gene expression**. The final product of gene expression is the synthesis of molecules called **proteins**, which exist in a wide variety of shapes and sizes, perform many different functions, and bestow upon neurons virtually all of their unique characteristics. **Protein synthesis**, the assembly of protein molecules, occurs in the cytoplasm. Because the DNA never leaves the nucleus, an intermediary must carry the genetic message to the sites of protein synthesis in the cytoplasm. This function is performed by another long molecule called **messenger ribonucleic acid**, or **mRNA**. mRNA consists of four different nucleic acids strung together in various sequences to form a chain. The detailed sequence of the nucleic acids in the chain represents the information in the gene, just as the sequence of letters gives meaning to a written word.

The process of assembling a piece of mRNA that contains the information of a gene is called **transcription**, and the resulting mRNA is called



▲ **FIGURE 2.8**
The internal structure of a typical neuron.



▲ **FIGURE 2.9**
Gene transcription. (a) RNA molecules are synthesized by RNA polymerase and then processed into mRNA to carry the genetic instructions for protein assembly from the nucleus to the cytoplasm. (b) Transcription is initiated at the promoter region of the gene and stopped at the terminator region. The initial RNA must be spliced to remove the introns that do not code for protein.

the *transcript* (Figure 2.9a). Interspersed between protein-coding genes are long stretches of DNA whose functions remain poorly understood. Some of these regions, however, are known to be important for regulating transcription. At one end of the gene is the **promoter**, the region where the RNA-synthesizing enzyme, *RNA polymerase*, binds to initiate transcription. The binding of the polymerase to the promoter is tightly regulated by other proteins called **transcription factors**. At the other end is a sequence of DNA called the *terminator*, or *stop sequence*, that the RNA polymerase recognizes as the end point for transcription.

In addition to the non-coding regions of DNA that flank the genes, there are often additional stretches of DNA within the gene itself that cannot be used to code for protein. These interspersed regions are called *introns*, and the coding sequences are called *exons*. Initial transcripts contain both introns and exons, but then, by a process called **RNA splicing**,

the introns are removed and the remaining exons are fused together (Figure 2.9b). In some cases, specific exons are also removed with the introns, leaving an “alternatively spliced” mRNA that actually encodes a different protein. Thus, transcription of a single gene can ultimately give rise to several different mRNAs and protein products.

mRNA transcripts emerge from the nucleus via pores in the nuclear envelope and travel to the sites of protein synthesis elsewhere in the neuron. At these sites, a protein molecule is assembled much as the mRNA molecule was: by linking together many small molecules into a chain. In the case of protein, the building blocks are **amino acids**, of which there are 20 different kinds. This assembling of proteins from amino acids under the direction of the mRNA is called **translation**.

The scientific study of this process, which begins with the DNA of the nucleus and ends with the synthesis of protein molecules in the cell, is known as *molecular biology*. The “central dogma” of molecular biology is summarized as follows:



Neuronal Genes, Genetic Variation, and Genetic Engineering. Neurons differ from other cells in the body because of the specific genes they express as proteins. A new understanding of these genes is now possible because the human **genome**—the entire length of DNA that comprises the genetic information in our chromosomes—has been sequenced. We now know the 25,000 “words” that comprise our genome, and we know where these genes can be found on each chromosome. Furthermore, we are learning which genes are expressed uniquely in neurons (Box 2.2). This knowledge has paved the way to understanding the genetic basis of many diseases of the nervous system. In some diseases, long stretches of DNA that contain several genes are missing; in others, genes are duplicated, leading to overexpression of specific proteins. These sorts of mishaps, called *gene copy number variations*, often occur at the moment of conception when paternal and maternal DNA mix to create the genome of the offspring. Some instances of serious psychiatric disorders, including autism and schizophrenia, were recently shown to be caused by gene copy number variations in the affected children. (Psychiatric disorders are discussed in Chapter 22.)

Other nervous system disorders are caused by *mutations*—“typographical errors”—in a gene or in the flanking regions of DNA that regulate the gene’s expression. In some cases, a single protein may be grossly abnormal or missing entirely, disrupting neuronal function. An example is fragile X syndrome, a disorder that manifests as intellectual disability and autism and is caused by disruption of a single gene (discussed further in Chapter 23). Many of our genes carry small mutations, called *single nucleotide polymorphisms*, which are analogous to a minor misspelling caused by a change in a single letter. These are usually benign, like the difference between “color” and “colour”—different spelling, same meaning. However, sometimes the mutations can affect protein function (consider the difference between “bear” and “bare”—same letters, different meaning). Such single nucleotide polymorphisms, alone or together with others, can affect neuronal function.

Genes make the brain, and understanding how they contribute to neuronal function in both healthy and diseased organisms is a major goal of neuroscience. An important breakthrough was the development of tools for **genetic engineering**—ways to change organisms by design with gene mutations or insertions. This technology has been used most in mice because they are rapidly reproducing mammals with a central nervous



BOX 2.2 BRAIN FOOD

Expressing One's Mind in the Post-Genomic Era

Sequencing the human genome was a truly monumental achievement, completed in 2003. The Human Genome Project identified all of the approximately 25,000 genes in human DNA. We now live in what has been called the “post-genomic era,” in which information about the genes expressed in our tissues can be used to diagnose and treat diseases. Neuroscientists are using this information to tackle long-standing questions about the biological basis of neurological and psychiatric disorders as well as to probe deeper into the origins of individuality. The logic goes as follows. The brain is a product of the genes expressed in it. Differences in gene expression between a normal brain and a diseased brain, or a brain of unusual ability, can be used to identify the molecular basis of the observed symptoms or traits.

The level of gene expression is usually defined as the number of mRNA transcripts synthesized by different cells and tissues to direct the synthesis of specific proteins. Thus, the analysis of gene expression requires comparing the relative abundance of various mRNAs in the brains of two groups of humans or animals. One way to perform such a comparison is to use DNA *microarrays*, which are created by robotic machines that arrange thousands of small spots of synthetic DNA on a microscope slide. Each spot contains a unique DNA sequence that will recognize and stick to a different specific mRNA sequence. To compare the gene expression in two brains, one begins by collecting a sample of mRNAs from each brain. The mRNA of one brain is labeled with a chemical tag that fluoresces green, and the mRNA of the other brain is labeled with a tag that fluoresces red. These samples are then applied to the microarray. Highly expressed genes will produce brightly fluorescent spots, and differences in the relative gene expression between the brains will be revealed by differences in the color of the fluorescence (Figure A).

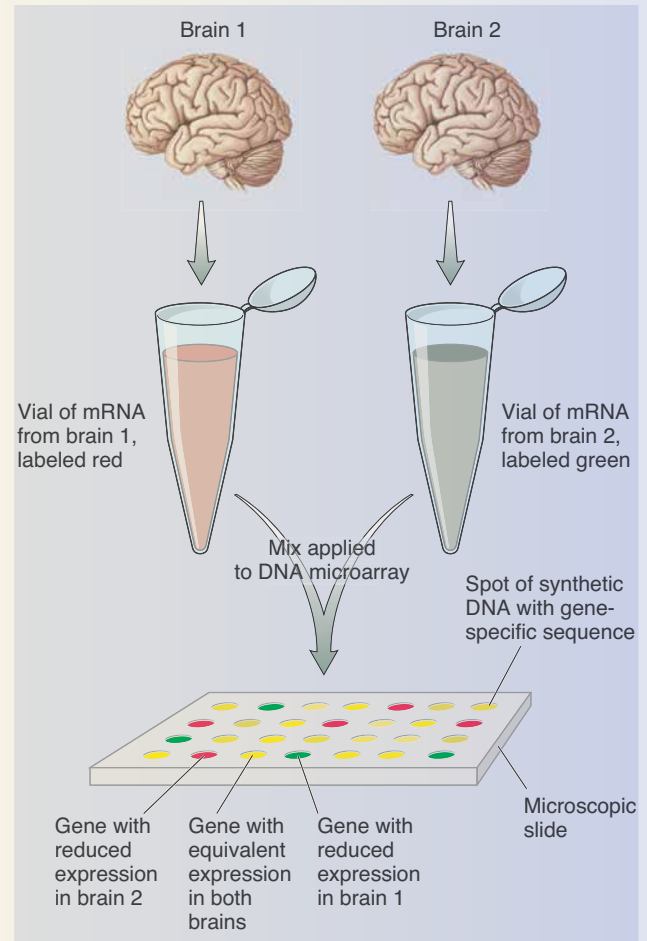


Figure A
Profiling differences in gene expression.

system similar to our own. Today, it is common in neuroscience to hear about **knockout mice**, in which one gene has been deleted (or “knocked out”). Such mice can be used to study the progression of a disease, like fragile X, with the goal of correcting it. Another approach has been to generate **transgenic mice**, in which genes have been introduced and overexpressed; these new genes are called *transgenes*. **Knock-in mice** have also been created in which the native gene is replaced with a modified transgene.

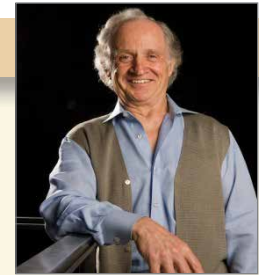
We will see many examples in this book of how genetically engineered animals have been used in neuroscience. The discoveries that allowed genetic modification of mice have revolutionized biology. The researchers who did this work were recognized with the 2007 Nobel Prize in Physiology or Medicine: Martin Evans of Cardiff University, Oliver Smithies of the University of North Carolina at Chapel Hill, and Mario Capecchi of the University of Utah (Box 2.3).



BOX 2.3 PATH OF DISCOVERY

Gene Targeting in Mice

by Mario Capecchi



How did I first get the idea to pursue gene targeting in mice? From a simple observation. Mike Wigler, now at Cold Spring Harbor Laboratory, and Richard Axel, at Columbia University, had published a paper in 1979 showing that exposing mammalian cells to a mixture of DNA and calcium phosphate would cause some cells to take up the DNA in functional form and express the encoded genes. This was exciting because they had clearly demonstrated that exogenous, functional DNA could be introduced into mammalian cells. But I wondered why their efficiency was so low. Was it a problem of delivery, insertion of exogenous DNA into the chromosome, or expression of the genes once inserted into the host chromosome? What would happen if purified DNA was directly injected into the nucleus of mammalian cells in culture?

To find out, I converted a colleague's electrophysiology station into a miniature hypodermic needle to directly inject DNA into the nucleus of a living cell using mechanical micro-manipulators and light microscopy (Figure A). The procedure worked with amazing efficiency (Capecchi, 1980). With this method, the frequency of successful integration was now one in three cells rather than one in a million cells as formerly. This high efficiency directly led to the development

of transgenic mice through the injection and random integration of exogenous DNA into chromosomes of fertilized mouse eggs, or zygotes. To achieve the high efficiency of expression of the exogenous DNA in the recipient cell, I had to attach small fragments of viral DNA, which we now understand to contain enhancers that are critical in eukaryotic gene expression.

But what fascinated me most was our observation that when many copies of a gene were injected into a cell nucleus, all of these molecules ended up in an ordered head-to-tail arrangement, called a *concatemer* (Figure B). This was astonishing and could not have occurred as a random event. We went on to unequivocally prove that homologous recombination, the process by which chromosomes share genetic information during cell division, was responsible for the incorporation of the foreign DNA (Folger et al., 1982). These experiments demonstrated that all mammalian somatic cells contain a very efficient machinery for swapping segments of DNA that have similar sequences of nucleotides. Injection of a thousand copies of a gene sequence into the nucleus of a cell resulted in chromosomal insertion of a concatemer containing a thousand copies of that sequence, all oriented in the same direction. This simple observation directly led me to

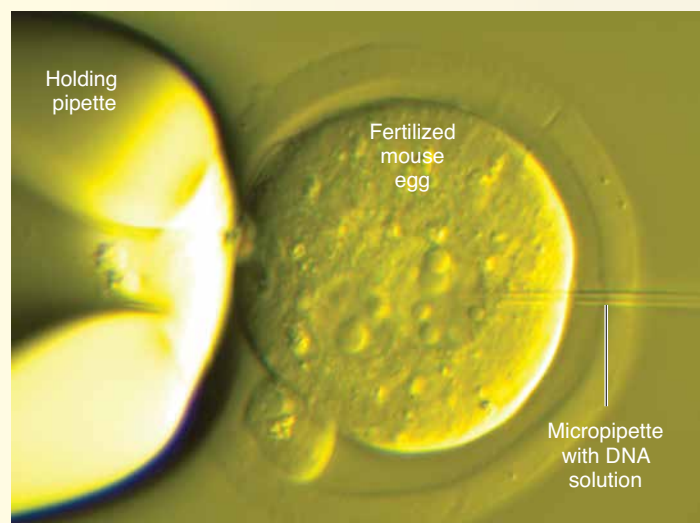


Figure A

Fertilized mouse egg receiving an injection of foreign DNA. (Image courtesy of Dr. Peimin Qi, Division of Comparative Medicine, Massachusetts Institute of Technology.)

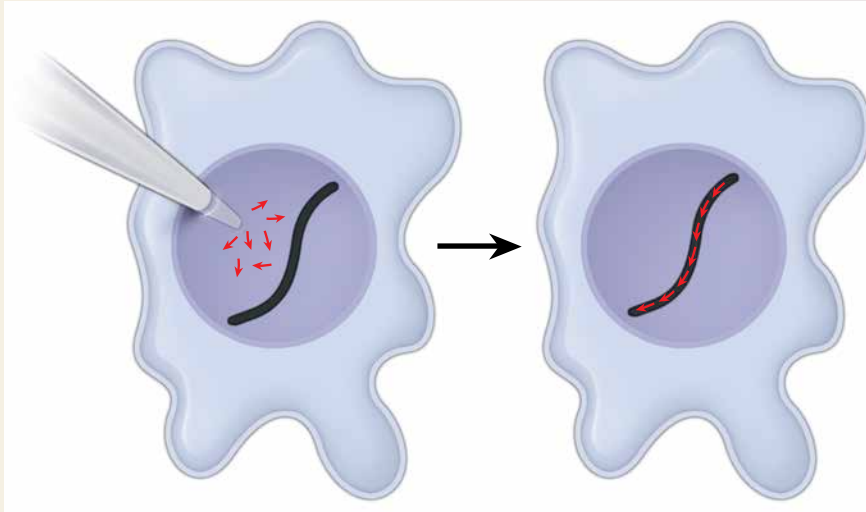


Figure B

envision mutating any chosen gene, in any chosen manner, in living mice by gene targeting.

Excited by this possibility, in 1980, I submitted a grant to the U.S. National Institutes of Health (NIH) proposing to directly alter gene DNA sequences in mammalian cultured cells by homologous recombination. They rejected the proposal, and their arguments were not unreasonable. They argued that the probability of the exogenously added DNA sequence ever finding the DNA sequence similar enough to enable homologous recombination in living mammalian cells (containing 3×10^9 nucleotide base pairs) was vanishingly small. Fortunately, my grant application contained two other proposals that the NIH reviewers liked, and they funded those projects. I used those funds to support the gene targeting project. Four years later, we had results supporting our ability to do gene targeting in cultured mammalian cells. I then resubmitted a new NIH grant application to the same review panel, now proposing to extend gene targeting to generating mutant mice. Their evaluation sheet in response began this way: "We are glad you didn't follow our advice."

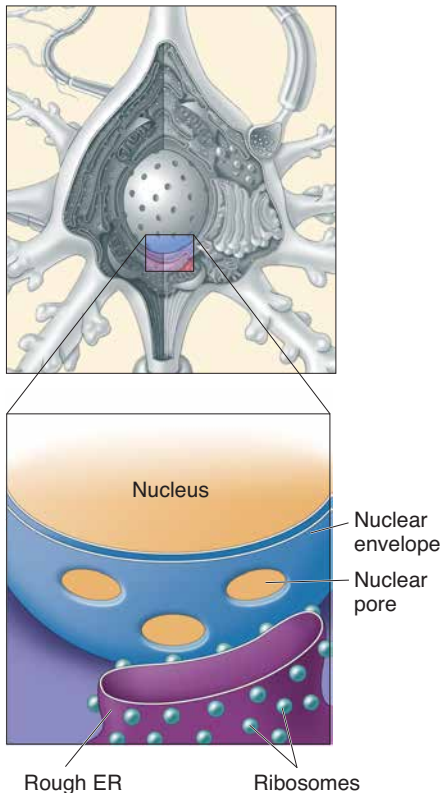
It took 10 years to develop gene targeting in mice (Thomas & Capecchi, 1987). Prior to this success, we had to understand the homologous recombination machinery in eukaryotic cells. Also, because the frequency of gene targeting was low, if we were to be successful in transferring our technology to mice, we needed mouse embryonic stem cells capable of contributing to the formation of the germ line—the sperm and eggs—in mature animals. I was getting depressed from our lack of success using cells derived from embryonal carcinoma

(EC). Then I heard a rumor that Martin Evans in Cambridge, England was isolating more promising cells, which he called *EK cells*, that resembled EC cells but were derived from a normal mouse embryo rather than from tumors. I called him and asked if the rumor was correct, and he said it was. My next question was whether I could come to his laboratory to learn how to work with those cells, and his answer again was yes. Christmas time, 1985, was beautiful in Cambridge. My wife, who worked with me, and I had a wonderful couple of weeks learning how to maintain these marvelous cells and use them to generate mice capable of germ line transmission.

Investigators often have a preconceived idea about the particular role of their gene of interest in mouse biology, and they are usually very surprised by results when the gene is knocked out. Gene targeting has taken us in many new directions, including most recently pursuing the role of microglia, cells that migrate into the brain after being generated in the bone marrow along with immune and blood cells. Mutating these cells in mice results in a pathology remarkably similar to the human condition called trichotillomania, a type of obsessive-compulsive disorder characterized by strong urges to pull out one's hair. Amazingly, transplanting normal bone marrow into mutant mice permanently cures them of this pathological behavior (Chen et al., 2010). Now, we are deeply immersed in trying to understand the mechanism of how microglia control neural circuit output and, more importantly, exploring the intimate relationship between the immune system (in this case microglia) and neuropsychiatric disorders such as depression, autism, schizophrenia, and Alzheimer's disease.

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▲ **FIGURE 2.10**
Rough endoplasmic reticulum, or rough ER.

Rough Endoplasmic Reticulum. Neurons make use of the information in genes by synthesizing proteins. Protein synthesis occurs at dense globular structures in the cytoplasm called **ribosomes**. mRNA transcripts bind to the ribosomes, and the ribosomes translate the instructions contained in the mRNA to assemble a protein molecule. In other words, ribosomes use the blueprint provided by the mRNA to manufacture proteins from raw material in the form of amino acids.

In neurons, many ribosomes are attached to stacks of membrane called **rough endoplasmic reticulum**, or **rough ER** (Figure 2.10). Rough ER abounds in neurons, far more than in glia or most other non-neuronal cells. In fact, we have already been introduced to rough ER by another name: Nissl bodies. This is the organelle stained with the dyes that Nissl introduced over 100 years ago.

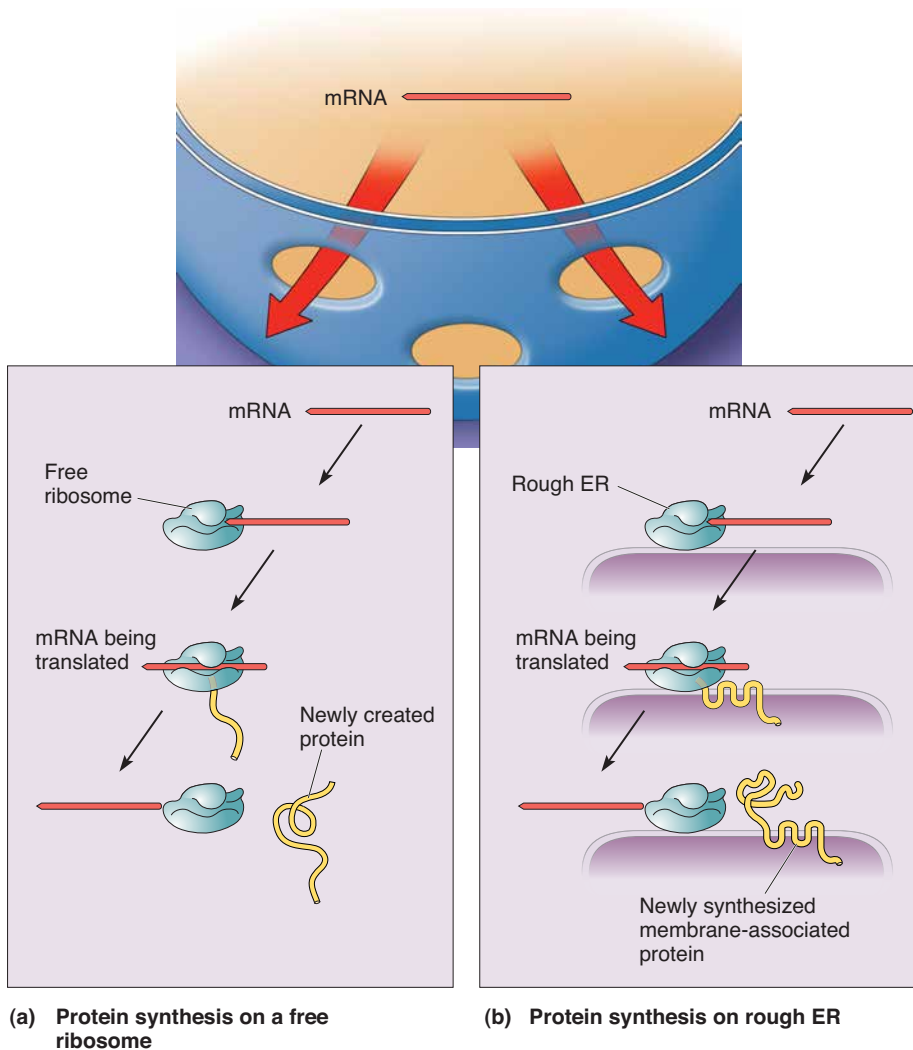
Rough ER is a major site of protein synthesis in neurons, but not all ribosomes are attached to rough ER. Many are freely floating and are called *free ribosomes*. Several free ribosomes may appear to be attached by a thread; these are called **polyribosomes**. The thread is a single strand of mRNA, and the associated ribosomes are working on it to make multiple copies of the same protein.

What is the difference between proteins synthesized on the rough ER and those synthesized on the free ribosomes? The answer appears to depend on the intended fate of the protein molecule. If it is destined to reside within the cytosol of the neuron, then the protein's mRNA transcript shuns the ribosomes of the rough ER and gravitates toward the free ribosomes (Figure 2.11a). However, if the protein is destined to be inserted into the membrane of the cell or an organelle, then it is synthesized on the rough ER. As the protein is being assembled, it is threaded back and forth through the membrane of the rough ER, where it is trapped (Figure 2.11b). It is not surprising that neurons have so much rough ER because, as we shall see in later chapters, special membrane proteins are what give these cells their remarkable information-processing abilities.

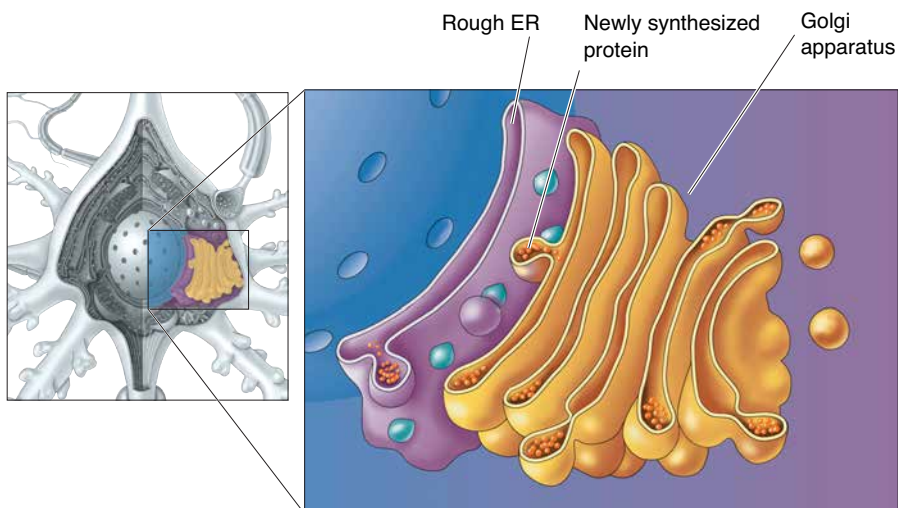
Smooth Endoplasmic Reticulum and the Golgi Apparatus. The remainder of the cytosol of the soma is crowded with stacks of membranous organelles that look a lot like rough ER without the ribosomes, so much so that one type is called **smooth endoplasmic reticulum**, or **smooth ER**. Smooth ER is heterogeneous and performs different functions in different locations. Some smooth ER is continuous with rough ER and is believed to be a site where the proteins that jut out from the membrane are carefully folded, giving them their three-dimensional structure. Other types of smooth ER play no direct role in the processing of protein molecules but instead regulate the internal concentrations of substances such as calcium. (This organelle is particularly prominent in muscle cells, where it is called *sarcoplasmic reticulum*, as we will see in Chapter 13.)

The stack of membrane-enclosed disks in the soma that lies farthest from the nucleus is the **Golgi apparatus**, first described in 1898 by Camillo Golgi (Figure 2.12). This is a site of extensive “post-translational” chemical processing of proteins. One important function of the Golgi apparatus is believed to be the sorting of certain proteins that are destined for delivery to different parts of the neuron, such as the axon and the dendrites.

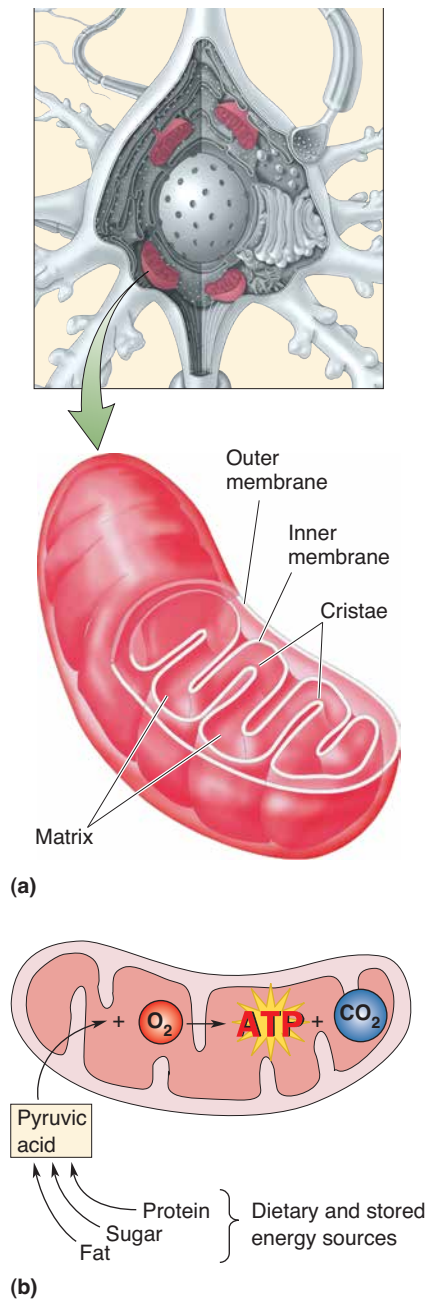
The Mitochondrion. Another very abundant organelle in the soma is the **mitochondrion** (plural: mitochondria). In neurons, these sausage-shaped structures are about 1 μm long. Within the enclosure of their outer membrane are multiple folds of inner membrane called *cristae* (singular: *crista*). Between the cristae is an inner space called *matrix* (Figure 2.13a).



◀ **FIGURE 2.11**
Protein synthesis on a free ribosome and on rough ER. mRNA binds to a ribosome, initiating protein synthesis. (a) Proteins synthesized on free ribosomes are destined for the cytosol. (b) Proteins synthesized on the rough ER are destined to be enclosed by or inserted into the membrane. Membrane-associated proteins are inserted into the membrane as they are assembled.



◀ **FIGURE 2.12**
The Golgi apparatus. This complex organelle sorts newly synthesized proteins for delivery to appropriate locations in the neuron.



▲ FIGURE 2.13

The role of mitochondria. (a) Components of a mitochondrion. (b) Cellular respiration. ATP is the energy currency that fuels biochemical reactions in neurons.

Mitochondria are the site of *cellular respiration* (Figure 2.13b). When a mitochondrion “inhales,” it pulls inside pyruvic acid (derived from sugars and digested proteins and fats) and oxygen, both of which are floating in the cytosol. Within the inner compartment of the mitochondrion, pyruvic acid enters into a complex series of biochemical reactions called the *Krebs cycle*, named after the German-British scientist Hans Krebs, who first proposed it in 1937. The biochemical products of the Krebs cycle provide energy that, in another series of reactions within the cristae (called the *electron-transport chain*), results in the addition of phosphate to adenosine diphosphate (ADP), yielding **adenosine triphosphate (ATP)**, the cell’s energy source. When the mitochondrion “exhales,” 17 ATP molecules are released for every molecule of pyruvic acid that had been taken in.

ATP is the energy currency of the cell. The chemical energy stored in ATP fuels most of the biochemical reactions of the neuron. For example, as we shall see in Chapter 3, special proteins in the neuronal membrane use the energy released by the breakdown of ATP into ADP to pump certain substances across the membrane to establish concentration differences between the inside and the outside of the neuron.

The Neuronal Membrane

The **neuronal membrane** serves as a barrier to enclose the cytoplasm inside the neuron and to exclude certain substances that float in the fluid that bathes the neuron. The membrane is about 5 nm thick and is studded with proteins. As mentioned earlier, some of the membrane-associated proteins pump substances from the inside to the outside. Others form pores that regulate which substances can gain access to the inside of the neuron. An important characteristic of neurons is that the protein composition of the membrane varies depending on whether it is in the soma, the dendrites, or the axon.

The function of neurons cannot be understood without understanding the structure and function of the membrane and its associated proteins. In fact, this topic is so important that we’ll spend much of the next four chapters looking at how the membrane endows neurons with the remarkable ability to transfer electrical signals throughout the brain and body.

The Cytoskeleton

Earlier, we compared the neuronal membrane to a circus tent draped over an internal scaffolding. This scaffolding is called the **cytoskeleton**, and it gives the neuron its characteristic shape. The “bones” of the cytoskeleton are the microtubules, microfilaments, and neurofilaments (Figure 2.14). Unlike the tent scaffolding, however, the cytoskeleton is not static. Elements of the cytoskeleton are dynamically regulated and are in continual motion. Your neurons are probably squirming around in your head even as you read this sentence.

Microtubules. Measuring 20 nm in diameter, **microtubules** are relatively large and run longitudinally down neurites. A microtubule appears as a straight, thick-walled hollow pipe. The wall of the pipe is composed of smaller strands that are braided like rope around the hollow core. Each of the smaller strands consists of the protein *tubulin*. A single tubulin molecule is small and globular; the strand consists of tubulins stuck together like pearls on a string. The process of joining small proteins to form a long strand is called *polymerization*; the resulting strand is called a *polymer*. Polymerization and depolymerization of microtubules and, therefore, of neuronal shape can be regulated by various signals within the neuron.

One class of proteins that participate in the regulation of microtubule assembly and function are *microtubule-associated proteins*, or *MAPs*. Among other functions (many of which are unknown), MAPs anchor the microtubules to one another and to other parts of the neuron. Pathological changes in an axonal MAP, called *tau*, have been implicated in the dementia that accompanies Alzheimer's disease (Box 2.4).

Microfilaments. Measuring only 5 nm in diameter, **microfilaments** are about the same thickness as the cell membrane. Found throughout the neuron, they are particularly numerous in the neurites. Microfilaments are braids of two thin strands that are polymers of the protein *actin*. Actin is one of the most abundant proteins in cells of all types, including neurons, and is believed to play a role in changing cell shape. Indeed, as we shall see in Chapter 13, actin filaments are critically involved in the mechanism of muscle contraction.

Like microtubules, actin microfilaments are constantly undergoing assembly and disassembly, and this process is regulated by signals in the neuron. In addition to running longitudinally down the core of the neurites like microtubules, microfilaments are also closely associated with the membrane. They are anchored to the membrane by attachments with a meshwork of fibrous proteins that line the inside of the membrane like a spider web.

Neurofilaments. With a diameter of 10 nm, **neurofilaments** are intermediate in size between microtubules and microfilaments. They exist in all cells of the body as *intermediate filaments*; only in neurons are they called *neurofilaments*. The difference in name reflects differences in structure among different tissues. For example, a different intermediate filament, keratin, composes hair when bundled together.

Of the types of fibrous structure we have discussed, neurofilaments most closely resemble the bones and ligaments of the skeleton. A neurofilament consists of multiple subunits (building blocks) that are wound together into a ropelike structure. Each strand of the rope consists of individual long protein molecules, making neurofilaments mechanically very strong.

The Axon

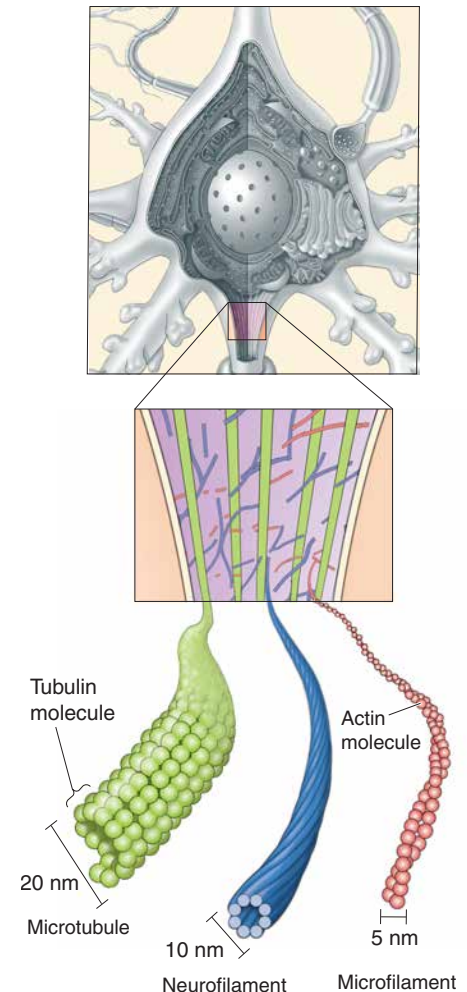
So far, we've explored the soma, organelles, membrane, and cytoskeleton. These structures are not unique to neurons but are found in all the cells in our body. Now we'll look at the axon, a structure found only in neurons and highly specialized for the transfer of information over distances in the nervous system.

The axon begins with a region called the **axon hillock**, which tapers away from the soma to form the initial segment of the axon proper (Figure 2.15). Two noteworthy features distinguish the axon from the soma:

1. No rough ER extends into the axon, and there are few, if any, free ribosomes in mature axons.
2. The protein composition of the axon membrane is fundamentally different from that of the soma membrane.

These structural differences translate into functional distinctions. Because there are no ribosomes, there is no protein synthesis in the axon. This means that all proteins in the axon must originate in the soma. And the different proteins in the axonal membrane enable it to serve as a wire that sends information over great distances.

Axons may extend from less than a millimeter to over a meter long. Axons often branch, and these branches, called **axon collaterals**, can



▲ **FIGURE 2.14**
Components of the cytoskeleton. The arrangement of microtubules, neurofilaments, and microfilaments gives the neuron its characteristic shape.



BOX 2.4 OF SPECIAL INTEREST

Alzheimer's Disease and the Neuronal Cytoskeleton

Neurites are the most remarkable structural feature of a neuron. Their elaborate branching patterns, critical for information processing, reflect the organization of the underlying cytoskeleton. It is therefore no surprise that a devastating loss of brain function can result when the cytoskeleton of neurons is disrupted. An example is *Alzheimer's disease*, which is characterized by the disruption of the cytoskeleton of neurons in the cerebral cortex, a region of the brain crucial for cognitive function. This disorder and its underlying brain pathology were first described in 1907 by the German physician A. Alzheimer in a paper titled "A Characteristic Disease of the Cerebral Cortex." Below are excerpts from the English translation.

One of the first disease symptoms of a 51-year-old woman was a strong feeling of jealousy toward her husband. Very soon she showed rapidly increasing memory impairments; she could not find her way about her home, she dragged objects to and fro, hid herself, or sometimes thought that people were out to kill her, then she would start to scream loudly.

During institutionalization her gestures showed a complete helplessness. She was disoriented as to time and place. From time to time she would state that she did not understand anything, that she felt confused and totally lost. Sometimes she considered the coming of the doctor as an official visit and apologized for not having finished her work, but other times she would start to yell in the fear that the doctor wanted to operate on her; or there were times that she would send him away in complete indignation, uttering phrases that indicated her fear that the doctor wanted to damage her woman's honor. From time to time she was completely delirious, dragging her blankets and sheets to and fro, calling for her husband and daughter, and seeming to have auditory hallucinations. Often she would scream for hours and hours in a horrible voice.

Mental regression advanced quite steadily. After four and a half years of illness the patient died. She was completely apathetic in the end, and was confined to bed in a fetal position. (Bick et al., 1987, pp. 1–2.)

Following her death, Alzheimer examined the woman's brain under the microscope. He made particular note of

changes in the "neurofibrils," elements of the cytoskeleton that can be stained by a silver solution.

The Bielschowsky silver preparation showed very characteristic changes in the neurofibrils. However, inside an apparently normal-looking cell, one or more single fibers could be observed that became prominent through their striking thickness and specific impregnability. At a more advanced stage, many fibrils arranged parallel showed the same changes. Then they accumulated forming dense bundles and gradually advanced to the surface of the cell. Eventually, the nucleus and cytoplasm disappeared, and only a tangled bundle of fibrils indicated the site where once the neuron had been located.

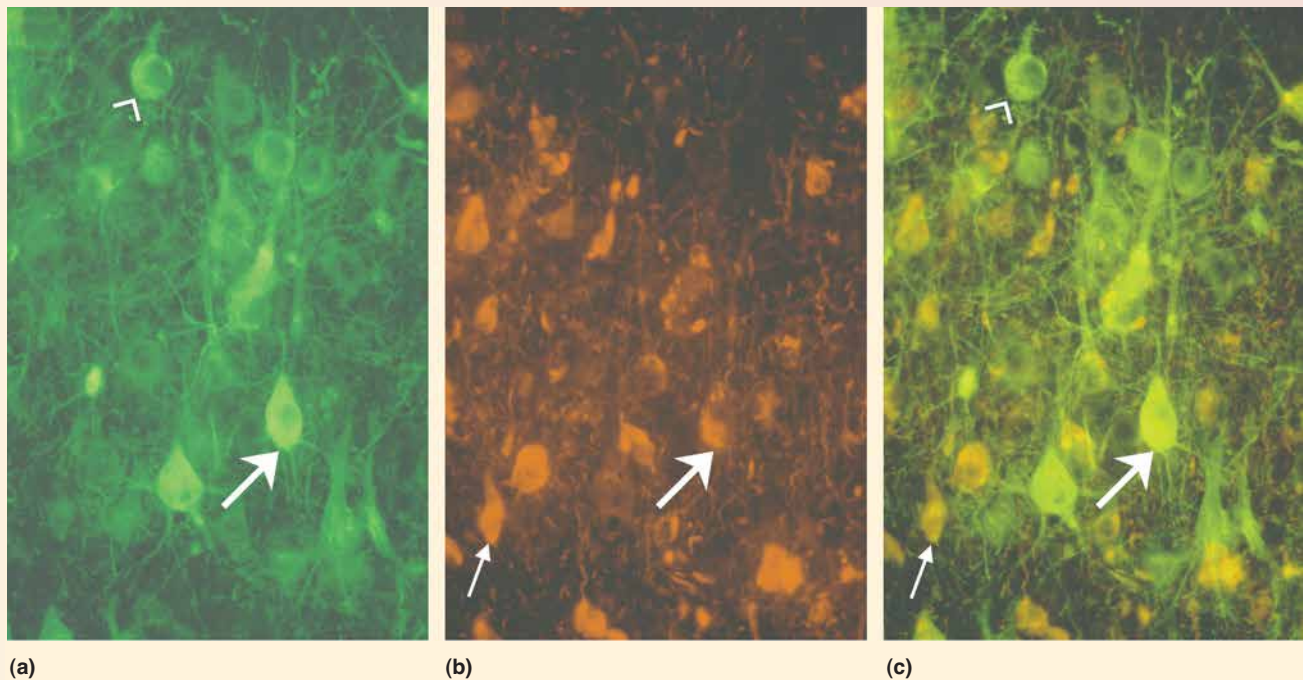
As these fibrils can be stained with dyes different from the normal neurofibrils, a chemical transformation of the fibril substance must have taken place. This might be the reason why the fibrils survived the destruction of the cell. It seems that the transformation of the fibrils goes hand in hand with the storage of an as yet not closely examined pathological product of the metabolism in the neuron. About one-quarter to one-third of all the neurons of the cerebral cortex showed such alterations. Numerous neurons, especially in the upper cell layers, had totally disappeared. (Bick et al., 1987, pp. 2–3.)

The severity of the dementia in Alzheimer's disease is well correlated with the number and distribution of what are now commonly known as *neurofibrillary tangles*, the "tombstones" of dead and dying neurons (Figure A). Indeed, as Alzheimer speculated, tangle formation in the cerebral cortex very likely causes the symptoms of the disease. Electron microscopy reveals that the major components of the tangles are *paired helical filaments*, long fibrous proteins braided together like strands of a rope (Figure B). It is now understood that these filaments consist of the microtubule-associated protein *tau*.

Tau normally functions as a bridge between the microtubules in axons, ensuring that they run straight and parallel to one another. In Alzheimer's disease, the tau detaches from the microtubules and accumulates in the soma. This disruption of the cytoskeleton causes the axons to wither, thus impeding the normal flow of information in the affected neurons.

travel long distances to communicate with different parts of the nervous system. Occasionally, an axon collateral returns to communicate with the same cell that gave rise to the axon or with the dendrites of neighboring cells. These axon branches are called *recurrent collaterals*.

The diameter of an axon is variable, ranging from less than 1 μm to about 25 μm in humans and to as large as 1 mm in squid. This variation in axon size is important. As will be explained in Chapter 4, the speed

**Figure A**

Neurons in a human brain with Alzheimer's disease. Normal neurons contain neurofilaments but no neurofibrillary tangles. **(a)** Brain tissue stained by a method that makes neuronal neurofilaments fluoresce green, showing viable neurons. **(b)** The same region of the brain stained to show the presence of tau within neurofibrillary tangles, revealed by red fluorescence. **(c)** Superimposition of images in parts **a** and **b**. The neuron indicated by the arrowhead contains neurofilaments but no tangles and therefore is healthy. The neuron indicated by the large arrow has neurofilaments but also has started to show accumulation of tau and therefore is diseased. The neuron indicated by the small arrow in parts **b** and **c** is dead because it contains no neurofilaments. The remaining tangle is the tombstone of a neuron killed by Alzheimer's disease. (Source: Courtesy of Dr. John Morrison and modified from Vickers et al., 1994.)

What causes such changes in tau? Attention has focused on another protein that accumulates in the brain of Alzheimer's patients, called *amyloid*. Alzheimer's disease research is moving very fast, but the consensus today is that the abnormal secretion of amyloid by neurons is the first step in a process

that leads to neurofibrillary tangle formation and dementia. Currently, hope for therapeutic intervention focuses on strategies to reduce the depositions of amyloid in the brain. The need for effective therapy is urgent: In the United States alone, more than 5 million people are afflicted with this tragic disease.



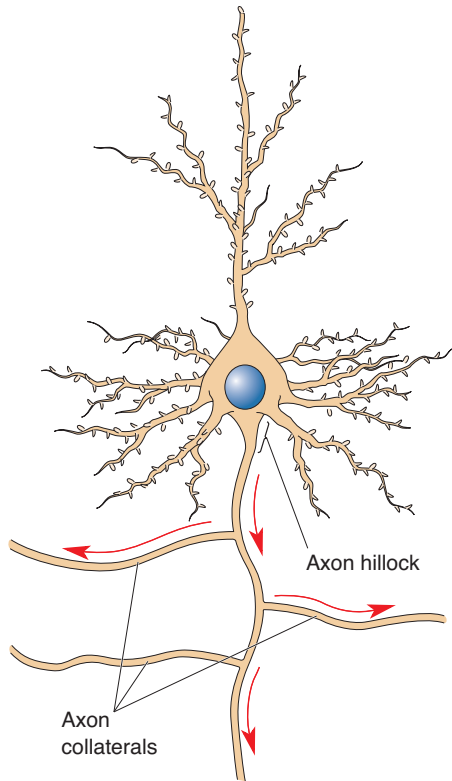
100 nm

Figure B

Paired helical filaments of a tangle.
(Source: Goedert, 1996, Fig. 2b.)

of the electrical signal that sweeps down the axon—the *nerve impulse*—depends on the axonal diameter. The thicker the axon, the faster the impulse travels.

The Axon Terminal. All axons have a beginning (the axon hillock), a middle (the axon proper), and an end. The end is called the **axon terminal** or **terminal bouton** (French for “button”), reflecting the fact that it usually



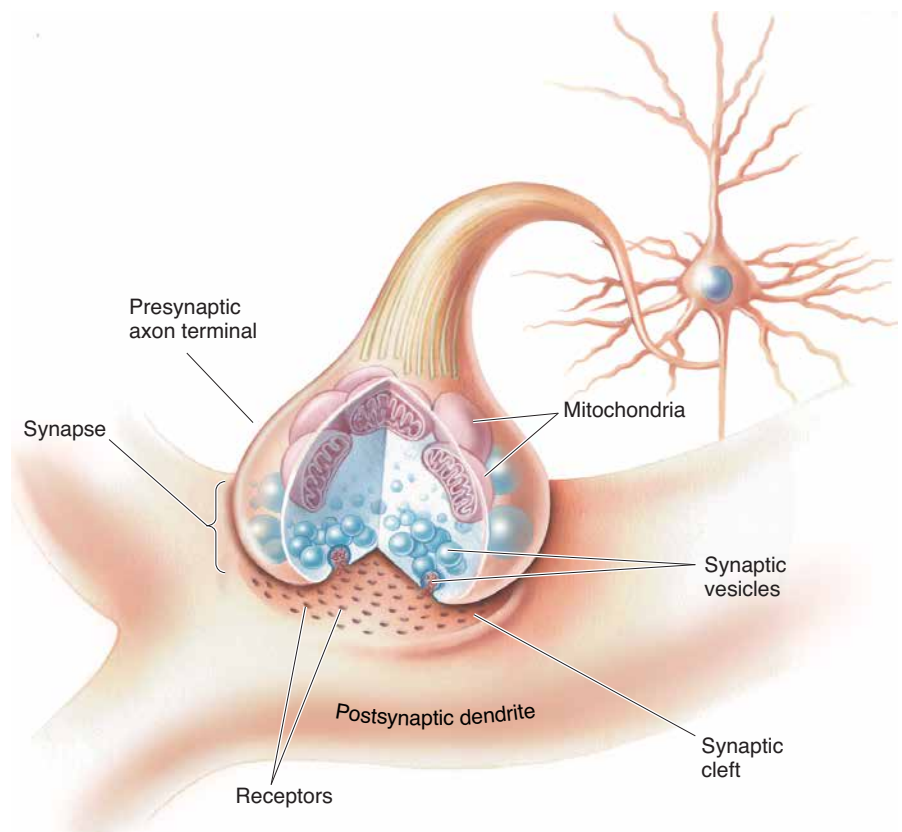
▲ FIGURE 2.15

The axon and axon collaterals. The axon functions like a telegraph wire to send electrical impulses to distant sites in the nervous system. The arrows indicate the direction of information flow.

appears as a swollen disk (Figure 2.16). The terminal is a site where the axon comes in contact with other neurons (or other cells) and passes information on to them. This point of contact is called the **synapse**, a word derived from the Greek, meaning “to fasten together.” Sometimes axons have many short branches at their ends, and each branch forms a synapse on dendrites or cell bodies in the same region. These branches are collectively called the **terminal arbor**. Sometimes axons form synapses at swollen regions along their length and then continue on to terminate elsewhere (Figure 2.17). Such swellings are called *boutons en passant* (“buttons in passing”). In either case, when a neuron makes synaptic contact with another cell, it is said to innervate that cell, or to provide **innervation**.

The cytoplasm of the axon terminal differs from that of the axon in several ways:

1. Microtubules do not extend into the terminal.
2. The terminal contains numerous small bubbles of membrane, called **synaptic vesicles**, that measure about 50 nm in diameter.
3. The inside surface of the membrane that faces the synapse has a particularly dense covering of proteins.
4. The axon terminal cytoplasm has numerous mitochondria, indicating a high energy demand.



▲ FIGURE 2.16

The axon terminal and the synapse. Axon terminals form synapses with the dendrites or somata of other neurons. When a nerve impulse arrives in the pre-synaptic axon terminal, neurotransmitter molecules are released from synaptic vesicles into the synaptic cleft. Neurotransmitter then binds to specific receptor proteins, causing the generation of electrical or chemical signals in the postsynaptic cell.

The Synapse. Although Chapters 5 and 6 are devoted entirely to how information is transferred from one neuron to another at the synapse, we'll preview the process here. The synapse has two sides: *presynaptic* and *postsynaptic* (see Figure 2.16). These names indicate the usual direction of information flow from “pre” to “post.” The presynaptic side generally consists of an axon terminal, whereas the postsynaptic side may be a dendrite or the soma of another neuron. The space between the presynaptic and postsynaptic membranes is called the **synaptic cleft**. The transfer of information at the synapse from one neuron to another is called **synaptic transmission**.

At most synapses, information in the form of electrical impulses traveling down the axon is converted in the terminal into a chemical signal that crosses the synaptic cleft. On the postsynaptic membrane, this chemical signal is converted again into an electrical one. The chemical signal, called a **neurotransmitter**, is stored in and released from the synaptic vesicles within the terminal. As we will see, different neurotransmitters are used by different types of neurons.

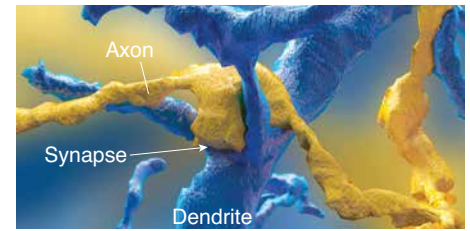
This electrical-to-chemical-to-electrical transformation of information makes possible many of the brain's computational abilities. Modification of this process is involved in memory and learning, and synaptic transmission dysfunction accounts for certain mental disorders. The synapse is also the site of action for many toxins and for most psychoactive drugs.

Axoplasmic Transport. As mentioned, one feature of the cytoplasm of axons, including the terminal, is the absence of ribosomes. Because ribosomes are the protein factories of the cell, their absence means that the proteins of the axon must be synthesized in the soma and then shipped down the axon. Indeed, in the mid-nineteenth century, English physiologist Augustus Waller showed that axons cannot be sustained when separated from their parent cell body. The degeneration of axons that occurs when they are cut is now called *Wallerian degeneration*. Because it can be detected with certain staining methods, Wallerian degeneration is one way to trace axonal connections in the brain.

Wallerian degeneration occurs because the normal flow of materials from the soma to the axon terminal is interrupted. This movement of material down the axon is called **axoplasmic transport**. This was first demonstrated directly by the experiments of American neurobiologist Paul Weiss and his colleagues in the 1940s. They found that if they tied a thread around an axon, material accumulated on the side of the knot closest to the soma. When the knot was untied, the accumulated material continued down the axon at a rate of 1–10 mm per day.

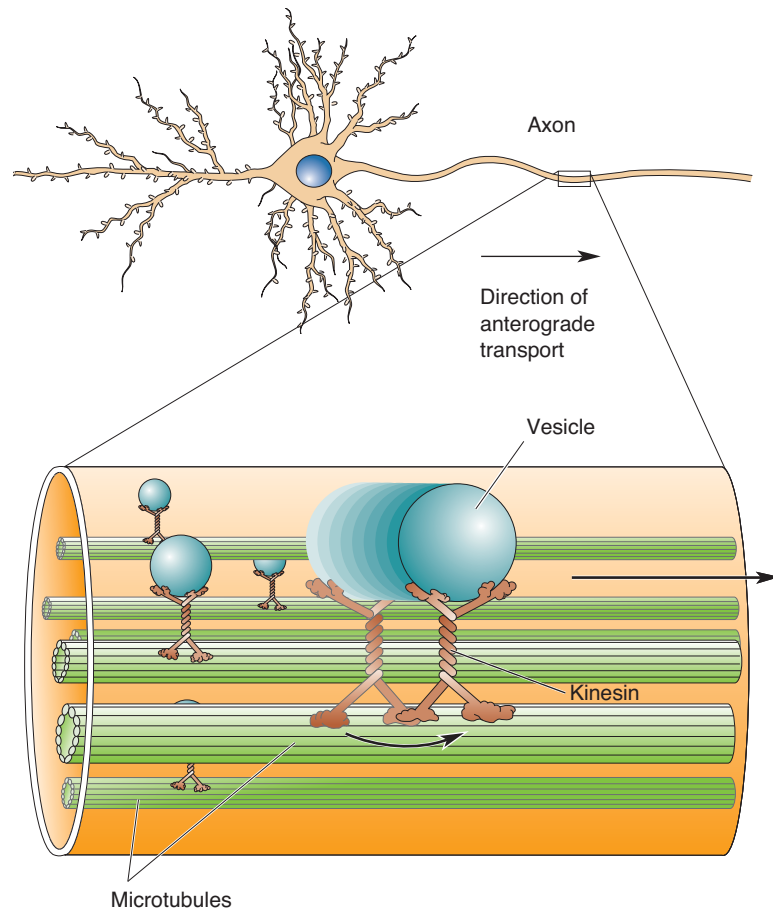
This was a remarkable discovery, but it is not the whole story. If all material moved down the axon by this transport mechanism alone, it would not reach the ends of the longest axons for at least half a year—too long a wait to feed hungry synapses. In the late 1960s, methods were developed to track the movements of protein molecules down the axon into the terminal. These methods entailed injecting the somata of neurons with radioactive amino acids. Recall that amino acids are the building blocks of proteins. The “hot” amino acids were assembled into proteins, and the arrival of radioactive proteins in the axon terminal was timed to calculate the rate of transport. This *fast axoplasmic transport* (so named to distinguish it from *slow axoplasmic transport* described by Weiss) occurred at a rate as high as 1,000 mm per day.

Much is now known about how fast axoplasmic transport works. Material is enclosed within vesicles, which then “walk down” the microtubules of the axon. The “legs” are provided by a protein called *kinesin*, and



▲ **FIGURE 2.17**

A bouton en passant. An axon (colored yellow) makes a synapse on a dendrite (colored blue) as they cross. This synapse was reconstructed from a series of images made using an electron microscope. (Source: Courtesy of Dr. Sebastian Seung, Princeton University, and Kris Krug, Pop Tech.)



▲ **FIGURE 2.18**

A mechanism for the movement of material on the microtubules of the axon.

Trapped in membrane-enclosed vesicles, material is transported from the soma to the axon terminal by the action of the protein kinesin, which “walks” along microtubules at the expense of ATP.

the process is fueled by ATP (Figure 2.18). Kinesin moves material only from the soma to the terminal. All movement of material in this direction is called **anterograde transport**.

In addition to anterograde transport, there is a mechanism for the movement of material up the axon from the terminal to the soma. This process is believed to provide signals to the soma about changes in the metabolic needs of the axon terminal. Movement in this direction, from terminal to soma, is called **retrograde transport**. The molecular mechanism is similar to anterograde transport, except the “legs” for retrograde transport are provided by a different protein, *dynein*. Both anterograde and retrograde transport mechanisms have been exploited by neuroscientists to trace connections in the brain (Box 2.5).

Dendrites

The term *dendrite* is derived from the Greek for “tree,” reflecting the fact that these neurites resemble the branches of a tree as they extend from the soma. The dendrites of a single neuron are collectively called a **dendritic tree**; each branch of the tree is called a *dendritic branch*. The wide variety of shapes and sizes of dendritic trees are used to classify different groups of neurons.

Because dendrites function as the antennae of the neuron, they are covered with thousands of synapses (Figure 2.19). The dendritic membrane



BOX 2.5 OF SPECIAL INTEREST

Hitching a Ride with Retrograde Transport

Fast anterograde transport of proteins in axons was shown by injecting the soma with radioactive amino acids. The success of this method immediately suggested a way to trace connections in the brain. For example, to determine where neurons in the eye send their axons elsewhere in the brain, the eye was injected with radioactive proline, an amino acid. The proline was incorporated into proteins in the somata that were then transported to the axon terminals. By use of a technique called *autoradiography*, the location of radioactive axon terminals could be detected, thereby revealing the extent of the connection between the eye and the brain.

Researchers subsequently discovered that retrograde transport could also be exploited to work out connections in the brain. Strangely enough, the enzyme horseradish peroxidase (HRP) is selectively taken up by axon terminals and then transported retrogradely to the soma. A chemical reaction can then be initiated to visualize the location of the HRP in slices of brain tissue after the experimental animal is euthanized. This method is commonly used to trace connections in the brain (Figure A).

Some viruses also exploit retrograde transport to infect neurons. For example, the oral type of herpesvirus enters axon terminals in the lips and mouth and is then transported back to the parent cell bodies. Here the virus usually remains dormant until physical or emotional stress occurs (as on a first date), at which time it replicates and returns to the nerve ending, causing a painful cold sore. Similarly, the rabies virus enters the nervous system by retrograde transport through

axons in the skin. However, once inside the soma, the virus wastes no time in replicating madly, killing its neuronal host. The virus is then taken up by other neurons within the nervous system, and the process repeats itself again and again, usually until the victim dies.

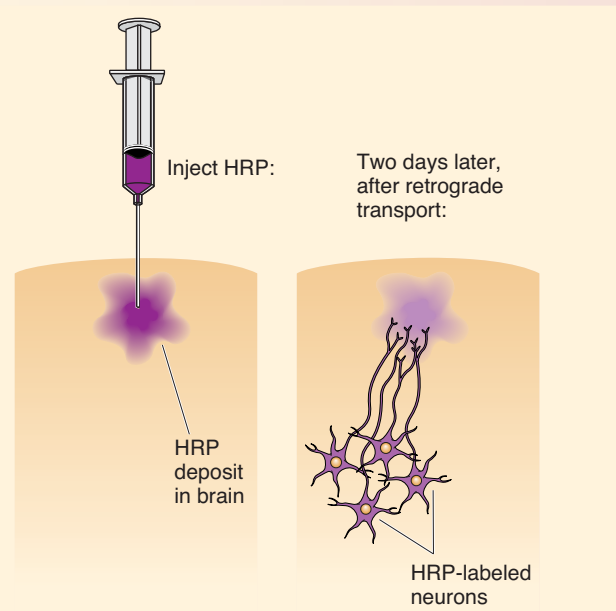
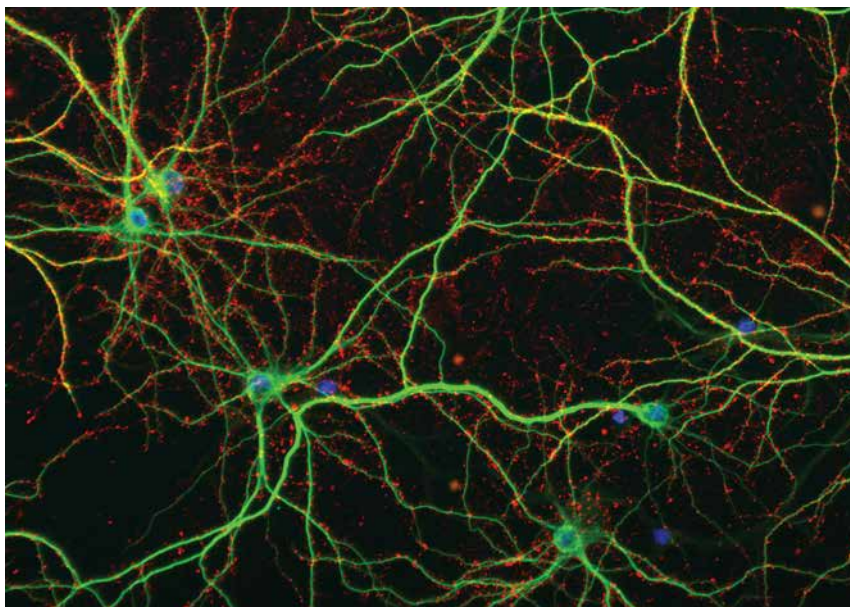


Figure A

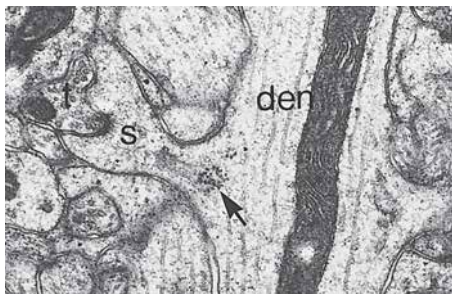


◀ FIGURE 2.19

Dendrites receiving synaptic inputs from axon terminals. Neurons have been made to fluoresce green using a method that reveals the distribution of a microtubule-associated protein. Axon terminals have been made to fluoresce orange-red using a method to reveal the distribution of synaptic vesicles. The nuclei are stained to fluoresce blue. (Source: Dr. Asha Bhakar, Massachusetts Institute of Technology.)



▲ **FIGURE 2.20**
Dendritic spines. This is a computer reconstruction of a segment of dendrite, showing the variable shapes and sizes of spines. Each spine is postsynaptic to one or two axon terminals. (Source: Harris & Stevens, 1989, cover image.)



▲ **FIGURE 2.21**
Postsynaptic polyribosomes. This electron micrograph shows a dendrite (den) with a cluster of polyribosomes (arrow) at the base of a dendritic spine (s) receiving a synapse from an axon terminal (t). (Source: Courtesy of Dr. Oswald Steward, University of California, Irvine.)

under the synapse (the *postsynaptic* membrane) has many specialized protein molecules called **receptors** that detect the neurotransmitters in the synaptic cleft.

The dendrites of some neurons are covered with specialized structures called **dendritic spines** that receive some types of synaptic input. Spines look like little punching bags that hang off the dendrite (Figure 2.20). The unusual morphology of spines has fascinated neuroscientists ever since their discovery by Cajal. They are believed to isolate various chemical reactions that are triggered by some types of synaptic activation. Spine structure is sensitive to the type and amount of synaptic activity. Unusual changes in spines have been shown to occur in the brains of individuals with cognitive impairments (Box 2.6).

For the most part, the cytoplasm of dendrites resembles that of axons. It is filled with cytoskeletal elements and mitochondria. One interesting difference is that polyribosomes can be observed in dendrites, often right under spines (Figure 2.21). Research has shown that synaptic transmission can actually direct local protein synthesis in some neurons. In Chapter 25, we will see that synaptic regulation of protein synthesis is crucial for information storage by the brain.

CLASSIFYING NEURONS

It is likely that we will never understand how each of the 85 billion neurons in the nervous system uniquely contributes to the function of the brain. But what if we could show that all the neurons in the brain can be categorized and that within each category all neurons function identically? The complexity of the problem might then be reduced to understanding the unique contribution of each category rather than each cell. With this hope, neuroscientists have devised schemes for classifying neurons.

Classification Based on Neuronal Structure

Efforts to classify neurons began in earnest with the development of the Golgi stain. These classification schemes, based on the morphology of dendrites, axons, and the structures they innervate, are still in wide use.

Number of Neurites. Neurons can be classified according to the total number of neurites (axons and dendrites) that extend from the soma (Figure 2.22). A neuron with a single neurite is said to be **unipolar**. If there are two neurites, the cell is **bipolar**, and if there are three or more, the cell is **multipolar**. Most neurons in the brain are **multipolar**.

Dendrites. Dendritic trees can vary widely from one type of neuron to another. Some have inspired names with flourish, like “double bouquet cells” or “chandelier cells.” Others have more utilitarian names, such as “alpha cells.” Classification is often unique to a particular part of the brain. For example, in the cerebral cortex (the structure that lies just under the surface of the cerebrum), there are two broad classes: **stellate cells** (star shaped) and **pyramidal cells** (pyramid shaped) (Figure 2.23).

Neurons can also be classified according to whether their dendrites have spines. Those that do are called **spiny**, and those that do not are called **aspinous**. These dendritic classification schemes can overlap. For example, in the cerebral cortex, all pyramidal cells are spiny. Stellate cells, on the other hand, can be either spiny or aspinous.



BOX 2.6 OF SPECIAL INTEREST

Intellectual Disability and Dendritic Spines

The elaborate architecture of a neuron's dendritic tree reflects the complexity of its synaptic connections with other neurons. Brain function depends on these highly precise synaptic connections, which are formed during the fetal period and are refined during infancy and early childhood. Not surprisingly, this very complex developmental process is vulnerable to disruption. Intellectual disability is said to have occurred if a disruption of brain development results in sub-average cognitive functioning that impairs adaptive behavior.

According to standardized tests, intelligence in the general population is distributed along a bell-shaped (Gaussian) curve. By convention, the mean intelligence quotient (IQ) is set at 100. About two-thirds of the total population falls within 15 points (one standard deviation) of the mean, and 95% of the population falls within 30 points (two standard deviations). People with intelligence scores below 70 are considered to be intellectually disabled if their cognitive impairment affects their ability to adapt their behavior to the setting in which they live. Some 2–3% of humans fit this description.

Intellectual disability has many causes. The most severe forms are associated with genetic disorders, such as a condition called *phenylketonuria (PKU)*. The basic abnormality is a deficit in the liver enzyme that metabolizes the dietary amino acid phenylalanine. Infants born with PKU have an abnormally high level of the amino acid in the blood and brain. If the condition goes untreated, brain growth is stunted and severe intellectual disability results. Another example is *Down syndrome*, which occurs when the fetus has an extra copy of chromosome 21, thus disrupting normal gene expression during brain development.

Another cause of intellectual disability is problems during pregnancy that can include a maternal infection, for example with German measles (rubella), and malnutrition. Children born to alcoholic mothers frequently have *fetal alcohol syndrome* comprising a constellation of developmental abnormalities that include intellectual disability. Other causes of intellectual disability are asphyxia of the infant during childbirth and environmental impoverishment—the lack of good nutrition, socialization, and sensory stimulation—during infancy.

Although some forms of intellectual disability have very clear physical correlates (e.g., stunted growth; abnormalities in the structure of the head, hands, and body), most cases have only behavioral manifestations. The brains of these individuals appear grossly normal. How, then, do we account for the profound cognitive impairment? An important clue came in the 1970s from the research of Miguel Marin-Padilla, working at Dartmouth College, and Dominick Purpura, working

at the Albert Einstein College of Medicine in New York City. Using the Golgi stain, they studied the brains of intellectually disabled children and discovered remarkable changes in dendritic structure. The dendrites of low-functioning children had many fewer dendritic spines, and the spines that they did have were unusually long and thin (Figure A). The extent of the spine changes was well correlated with the degree of intellectual disability.

Dendritic spines are an important target of synaptic input. Purpura pointed out that the dendritic spines of intellectually disabled children resemble those of the normal human fetus. He suggested that intellectual disability reflects the failure of normal circuits to form in the brain. In the three decades since this seminal work was published, it was established that normal synaptic development, including maturation of the dendritic spines, depends critically on the environment during infancy and early childhood. An impoverished environment during an early critical period of development can lead to profound changes in the circuits of the brain. However, there is some good news. Many of the deprivation-induced changes in the brain can be reversed if intervention occurs early enough. In Chapter 23, we will take a closer look at the role of experience in brain development.

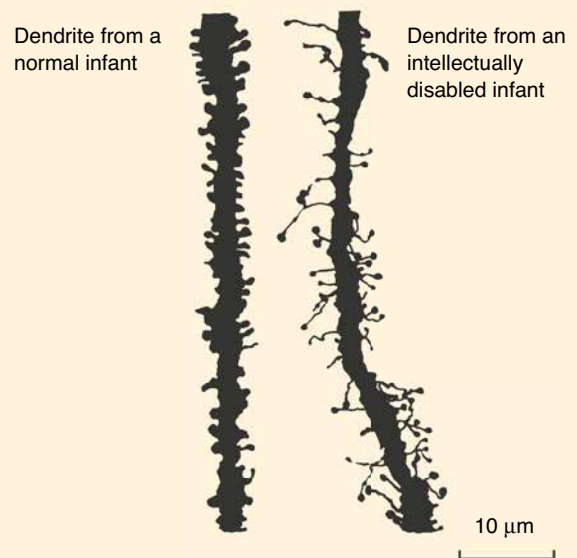
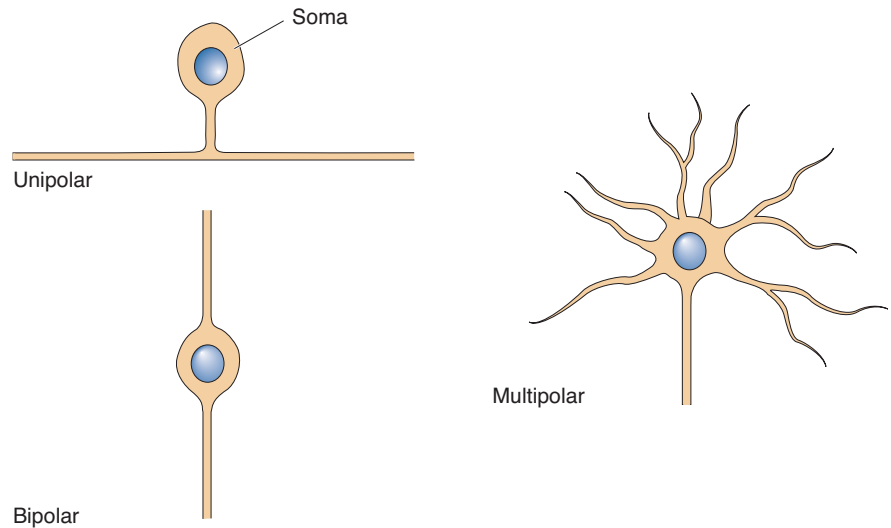


Figure A
Normal and abnormal dendrites. (Source: Purpura, 1974, Fig. 2A.)



▲ FIGURE 2.22

Classification of neurons based on the number of neurites.

Connections. Information is delivered to the nervous system by neurons that have neurites in the sensory surfaces of the body, such as the skin and the retina of the eye. Cells with these connections are called **primary sensory neurons**. Other neurons have axons that form synapses with the muscles and command movements; these are called **motor neurons**. But most neurons in the nervous system form connections only with other neurons. In this classification scheme, these cells are called **interneurons**.

Axon Length. Some neurons have long axons that extend from one part of the brain to the other; these are called *Golgi type I neurons*, or *projection neurons*. Other neurons have short axons that do not extend beyond the vicinity of the cell body; these are called *Golgi type II neurons*, or *local circuit neurons*. In the cerebral cortex, for example, pyramidal cells usually have long axons that extend to other parts of the brain and are therefore Golgi type I neurons. In contrast, stellate cells have axons that never extend beyond the cerebral cortex and are therefore Golgi type II neurons.

Classification Based on Gene Expression

We now understand that most differences between neurons ultimately can be explained at the genetic level. For example, differences in gene expression cause pyramidal cells and stellate cells to develop different shapes. Once a genetic difference is known, that information can be used to create transgenic mice that allow detailed investigation of neurons in this class. For example, a foreign gene encoding a fluorescent protein can be introduced and placed under the control of a cell type–specific gene promoter. **Green fluorescent protein** (usually simply abbreviated as **GFP**), encoded by a gene discovered in jellyfish, is used commonly in neuroscience research. When illuminated with the appropriate wavelength of light, the GFP fluoresces bright green, allowing visualization of the neuron in which it is expressed. Genetic engineering methods are now commonly used for measuring and manipulating the functions of neurons in different categories (Box 2.7).

We have known for some time that one important way neurons differ is the neurotransmitter they use. Neurotransmitter differences arise because of differences in the expression of proteins involved in transmitter

synthesis, storage, and use. Understanding these genetic differences enables a classification of neurons based on their neurotransmitters. For example, the motor neurons that command voluntary movements all release the neurotransmitter *acetylcholine* at their synapses; these motor cells are therefore also classified as *cholinergic*, meaning that they express the genes that enable use of this particular neurotransmitter. Collections of cells that use the same neurotransmitter make up the brain's neurotransmitter systems (see Chapters 6 and 15).

GLIA

Although most of this chapter is about neurons, as justified by the current state of knowledge, some neuroscientists consider glia the “sleeping giants” of neuroscience. Indeed, we continue to learn that glia contribute much more importantly to information processing in the brain than has been historically appreciated. Nevertheless, the data continue to indicate that glia contribute to brain function mainly by supporting neuronal functions. Although their role may be subordinate, without glia, the brain could not function properly.

Astrocytes

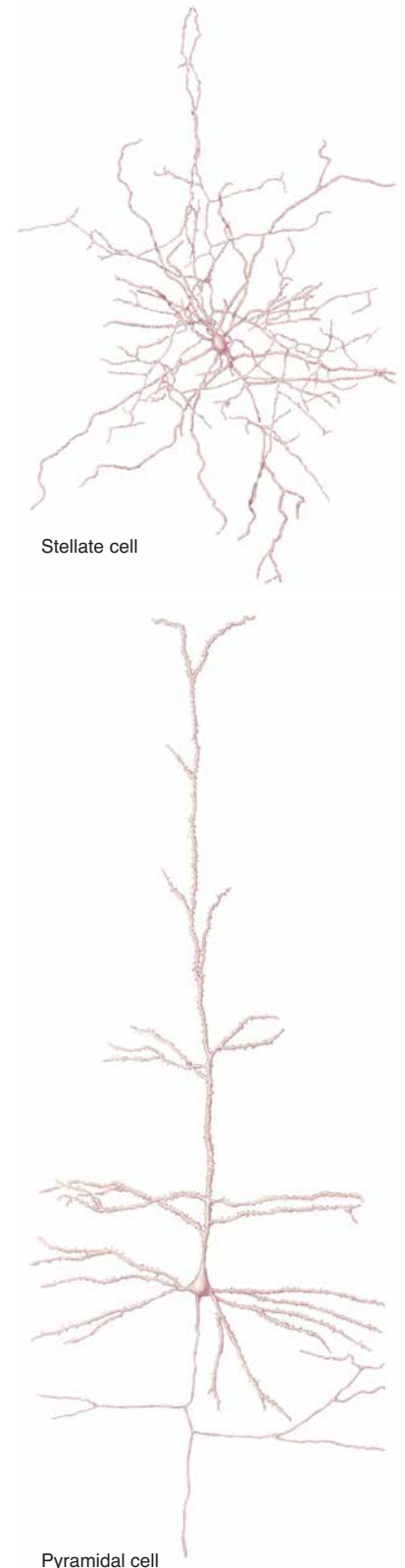
The most numerous glia in the brain are called **astrocytes** (Figure 2.24). These cells fill most of the spaces between neurons. The space that remains between neurons and astrocytes in the brain is only about 20 nm wide. Consequently, astrocytes probably influence whether a neurite can grow or retract.

An essential role of astrocytes is regulating the chemical content of this *extracellular space*. For example, astrocytes envelop synaptic junctions in the brain (Figure 2.25), thereby restricting the spread of neurotransmitter molecules that have been released. Astrocytes also have special proteins in their membranes that actively remove many neurotransmitters from the synaptic cleft. A recent and unexpected discovery is that astrocytic membranes also possess neurotransmitter receptors that, like the receptors on neurons, can trigger electrical and biochemical events inside the glial cell. Besides regulating neurotransmitters, astrocytes also tightly control the extracellular concentration of several substances that could interfere with proper neuronal function. For example, astrocytes regulate the concentration of potassium ions in the extracellular fluid.

Myelinating Glia

Unlike astrocytes, the primary function of **oligodendroglial** and **Schwann cells** is clear. These glia provide layers of membrane that insulate axons. Boston University anatomist Alan Peters, a pioneer in the electron microscopic study of the nervous system, showed that this wrapping, called **myelin**, spirals around axons in the brain (Figure 2.26). Because the axon fits inside the spiral wrapping like a sword in its scabbard, the name *myelin sheath* describes the entire covering. The sheath is interrupted periodically, leaving a short length where the axonal membrane is exposed. This region is called a **node of Ranvier** (Figure 2.27).

We will see in Chapter 4 that myelin serves to speed the propagation of nerve impulses down the axon. Oligodendroglia and Schwann cells differ in their location and some other characteristics. For example, oligodendroglia are found only in the central nervous system (brain and spinal cord), whereas Schwann cells are found only in the peripheral nervous



▲ **FIGURE 2.23**
Classification of neurons based on dendritic tree structure. Stellate cells and pyramidal cells, distinguished by the arrangement of their dendrites, are two types of neurons found in the cerebral cortex.



BOX 2.7 BRAIN FOOD

Understanding Neuronal Structure and Function with Incredible Cre

One type of cell in the body can be distinguished from another by the unique pattern of genes it expresses as proteins. Similarly, different classes of neurons in the brain can be identified based on which genes are expressed. With modern methods of genetic engineering, knowledge that a gene is uniquely expressed in one type of neuron can help determine the contributions of this cell type to brain function.

Let's consider as an example the neurons that uniquely express the gene encoding the protein choline acetyltransferase (ChAT). ChAT is an enzyme that synthesizes the neurotransmitter acetylcholine. It is only expressed in "cholinergic neurons" that use acetylcholine because only these neurons have the transcription factors that act on this gene's

promoter. If we insert into a mouse's genome a transgene engineered to be under the control of the same promoter, this foreign transgene will also be expressed only in cholinergic neurons. If the transgene expresses the enzyme Cre recombinase, derived from a bacterial virus, we can compel these cholinergic neurons to give up their secrets in myriad ways. Let's examine how.

Cre recombinase recognizes short DNA sequences called *loxP sites* that can be inserted on either side of another gene. The DNA between the *loxP sites* is said to be *floxed*. The Cre recombinase functions to cut out, or excise, the gene between the *loxP sites*. By breeding the "Cre mouse" with the "floxed mouse," one can generate mice in which a gene is deleted only in one particular type of neuron.

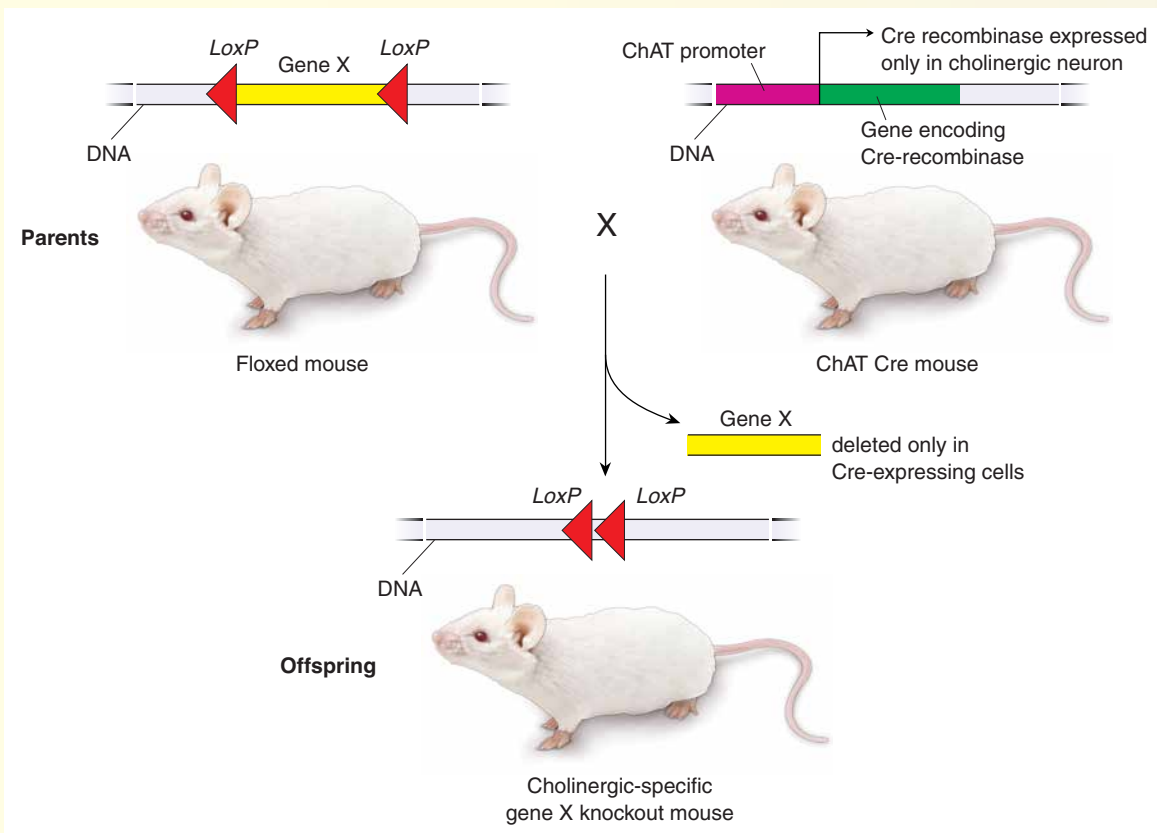


Figure A

Creating a mouse with a gene knockout only in cholinergic neurons is accomplished by crossing a floxed mouse with the gene of interest (gene X) flanked by *loxP* sites with another mouse in which Cre recombinase is under the control of the ChAT promoter. In the offspring, gene X is cut out only in the cells expressing Cre, namely, the cholinergic neurons.

In a simple example, we can ask how cholinergic neurons react to the deletion of another gene they normally express; let's call this gene X. To answer this question, we cross mice that have had gene X floxed (the "floxed mice") with our mice that express Cre under the control of the ChAT promoter (the "ChAT-Cre mice"). In the offspring, the floxed gene is removed only in those neurons that express Cre; that is, only in the cholinergic neurons (Figure A).

We can also use Cre to cause expression of novel transgenes in cholinergic neurons. Normally, expression of a transgene requires that we include a promoter sequence upstream of the protein-coding region. Transcription of the transgene fails to occur if a stop sequence is inserted between this promoter and the protein-coding sequence. Now consider what happens if we generate a transgenic mouse with this stop sequence flanked by loxP sites. Crossing this

mouse with our ChAT-Cre mouse generates offspring in which the transgene is expressed *only* in cholinergic neurons because the stop sequence has been removed only in these neurons (Figure B).

If we design this transgene to encode a fluorescent protein, we can use fluorescence to examine the structure and connections of these cholinergic neurons. If we design this transgene to express a protein that fluoresces only when impulses are generated by the neurons, we can monitor the activity of the cholinergic neurons by measuring light flashes. If we design this transgene to express a protein that kills or silences the neuron, we can see how brain function is altered in the absence of cholinergic neurons. The possible manipulations of cholinergic neurons through this feat of genetic engineering are limited only by the imagination of the scientist.

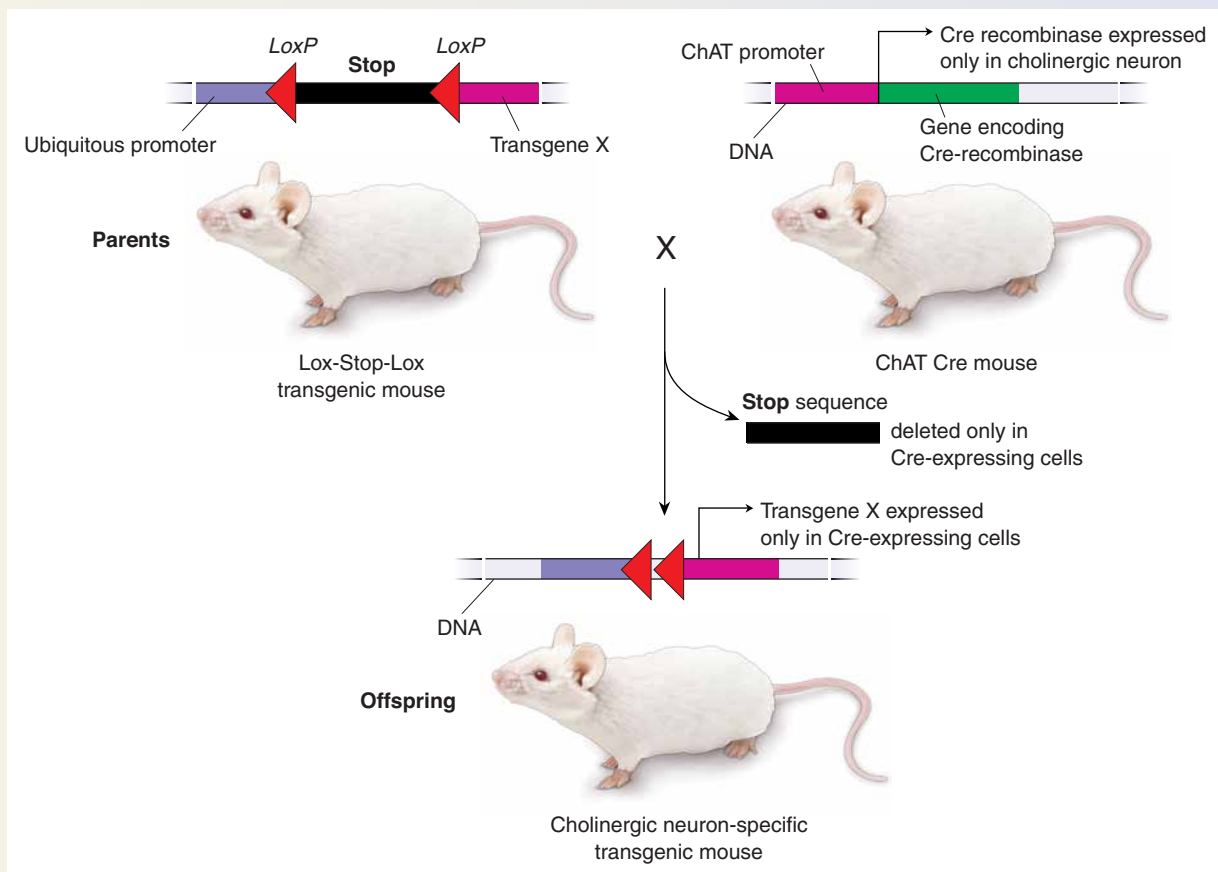


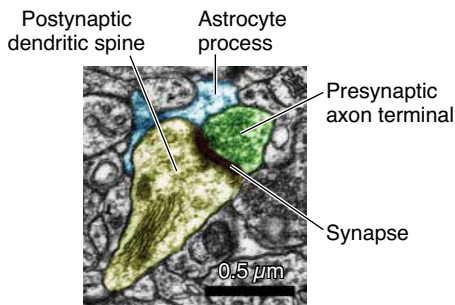
Figure B

A transgene of interest (transgene X) can also be expressed exclusively in cholinergic neurons. First, a mouse is created in which expression of the transgene is prevented by insertion of a floxed stop sequence between a strong, ubiquitous promoter and the coding region of the gene. Crossing this mouse with the ChAT-Cre mouse results in offspring in which the stop sequence has been deleted only in cholinergic neurons, allowing expression of the transgene only in these neurons.



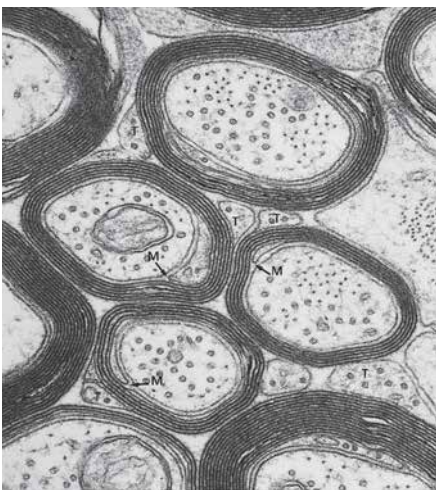
▲ FIGURE 2.24

An astrocyte. Astrocytes fill most of the space in the brain that is not occupied by neurons and blood vessels.



▲ FIGURE 2.25

Astrocytes envelop synapses. An electron micrograph of a thin slice through a synapse showing the presynaptic axon terminal and the postsynaptic dendritic spine (colored green) and an astrocyte process (colored blue) that wraps around them and restricts the extracellular space. (Source: Courtesy of Drs. Cagla Eroglu and Chris Risher, Duke University.)



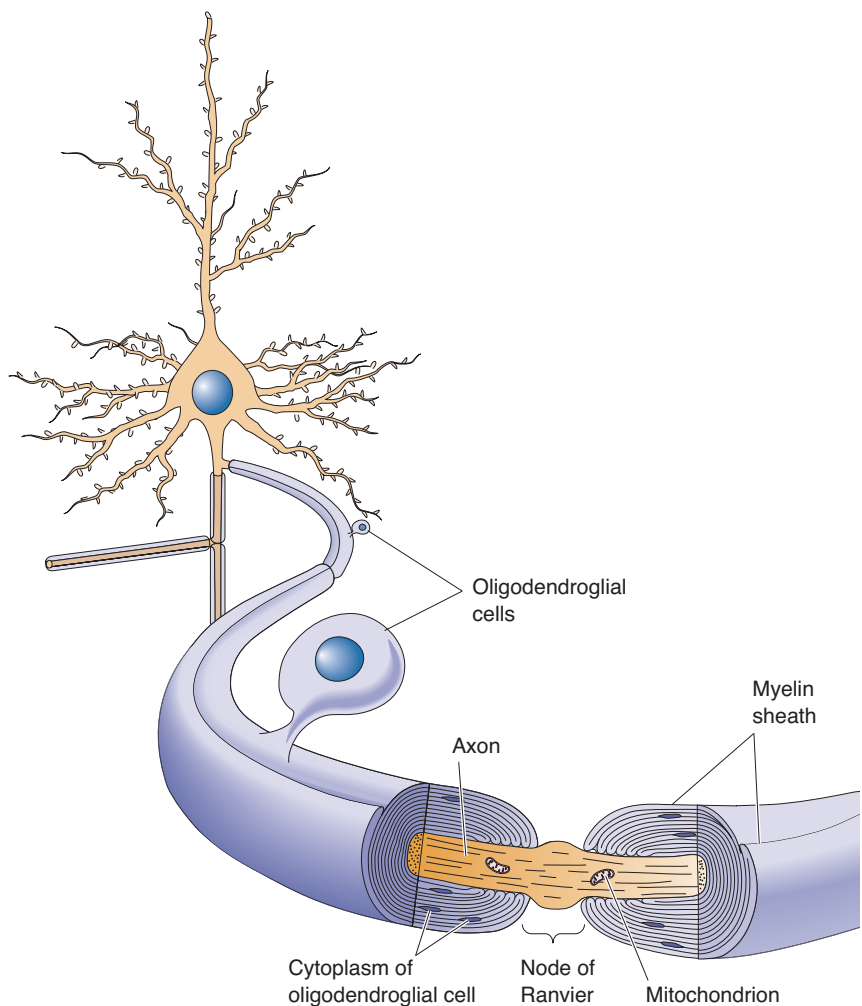
▲ FIGURE 2.26

Myelinated optic nerve fibers cut in cross section. (Source: Courtesy of Dr. Alan Peters.)

system (parts outside the skull and vertebral column). Another difference is that one oligodendroglial cell contributes myelin to several axons, whereas each Schwann cell myelinates only a single axon.

Other Non-Neuronal Cells

Even if we eliminated every neuron, every astrocyte, and every oligodendroglial cell, other cells would still remain in the brain. First, special cells called **ependymal cells** line fluid-filled ventricles within the brain and play a role in directing cell migration during brain development. Second, a class of cells called **microglia** function as phagocytes to remove debris left by dead or degenerating neurons and glia. Microglia have attracted much interest recently, as they appear to be involved in remodeling synaptic connections by gobbling them up. As we saw in Box 2.3, microglia can migrate into the brain from the blood, and disruption of this microglial invasion can interfere with brain functions and behavior. Finally, in addition to glial and ependymal cells, the brain also has vasculature: arteries, veins, and capillaries that deliver via the blood essential nutrients and oxygen to neurons.



▲ FIGURE 2.27

An oligodendroglial cell. Like the Schwann cells found in the nerves of the body, oligodendroglia provide myelin sheaths around axons in the brain and spinal cord. The myelin sheath of an axon is interrupted periodically at the nodes of Ranvier.

CONCLUDING REMARKS

Learning the structural characteristics of the neuron provides insight into how neurons and their different parts work because structure correlates with function. For example, the absence of ribosomes in the axon correctly predicts that proteins in the axon terminal are provided from the soma via axoplasmic transport. A large number of mitochondria in the axon terminal correctly predicts a high energy demand. The elaborate structure of the dendritic tree appears ideally suited for receiving incoming information, and indeed, this is where most of the synapses are formed with the axons of other neurons.

From the time of Nissl, the rough ER has been recognized as an important feature of neurons. What does this tell us about neurons? Recall that rough ER is a site of the synthesis of proteins destined to be inserted into the membrane. We will next see how the various proteins in the neuronal membrane give rise to the unique capabilities of neurons to transmit, receive, and store information.



KEY TERMS

Introduction

neuron (p. 24)
glial cell (p. 24)

The Neuron Doctrine

histology (p. 25)
Nissl stain (p. 25)
cytoarchitecture (p. 25)
Golgi stain (p. 26)
cell body (p. 26)
soma (p. 26)
perikaryon (p. 26)
neurite (p. 26)
axon (p. 26)
dendrite (p. 26)
neuron doctrine (p. 27)

The Prototypical Neuron

cytosol (p. 29)
organelle (p. 29)
cytoplasm (p. 29)
nucleus (p. 29)
chromosome (p. 29)
DNA (deoxyribonucleic acid) (p. 29)
gene (p. 29)
gene expression (p. 29)
protein (p. 29)
protein synthesis (p. 29)
mRNA (messenger ribonucleic acid) (p. 29)
transcription (p. 29)
promoter (p. 31)

transcription factor (p. 31)
RNA splicing (p. 31)
amino acid (p. 32)
translation (p. 32)
genome (p. 32)
genetic engineering (p. 32)
knockout mice (p. 33)
transgenic mice (p. 33)
knock-in mice (p. 33)
ribosome (p. 36)
rough endoplasmic reticulum (rough ER) (p. 36)
polyribosome (p. 36)
smooth endoplasmic reticulum (smooth ER) (p. 36)
Golgi apparatus (p. 36)
mitochondrion (p. 36)
ATP (adenosine triphosphate) (p. 38)
neuronal membrane (p. 38)
cytoskeleton (p. 38)
microtubule (p. 38)
microfilament (p. 39)
neurofilament (p. 39)
axon hillock (p. 39)
axon collateral (p. 39)
axon terminal (p. 41)
terminal bouton (p. 41)
synapse (p. 42)
terminal arbor (p. 42)
innervation (p. 42)
synaptic vesicle (p. 42)

synaptic cleft (p. 43)
synaptic transmission (p. 43)
neurotransmitter (p. 43)
axoplasmic transport (p. 43)
anterograde transport (p. 44)
retrograde transport (p. 44)
dendritic tree (p. 44)
receptor (p. 46)
dendritic spine (p. 46)

Classifying Neurons

unipolar neuron (p. 46)
bipolar neuron (p. 46)
multipolar neuron (p. 46)
stellate cell (p. 46)
pyramidal cell (p. 46)
spiny neuron (p. 46)
aspinous neuron (p. 46)
primary sensory neuron (p. 48)
motor neuron (p. 48)
interneuron (p. 48)
green fluorescent protein (GFP) (p. 48)

Glia

astrocyte (p. 49)
oligodendroglial cell (p. 49)
Schwann cell (p. 49)
myelin (p. 49)
node of Ranvier (p. 49)
ependymal cell (p. 52)
microglial cell (p. 52)



REVIEW QUESTIONS

1. State the neuron doctrine in a single sentence. To whom is this insight credited?
2. Which parts of a neuron are shown by a Golgi stain that are not shown by a Nissl stain?
3. What are three physical characteristics that distinguish axons from dendrites?
4. Of the following structures, state which ones are unique to neurons and which are not: nucleus, mitochondria, rough ER, synaptic vesicle, Golgi apparatus.
5. What are the steps by which the information in the DNA of the nucleus directs the synthesis of a membrane-associated protein molecule?
6. Colchicine is a drug that causes microtubules to break apart (depolymerize). What effect would this drug have on anterograde transport? What would happen in the axon terminal?
7. Classify the cortical pyramidal cell based on (1) the number of neurites, (2) the presence or absence of dendritic spines, (3) connections, and (4) axon length.
8. Knowledge of genes uniquely expressed in a particular category of neurons can be used to understand how those neurons function. Give one example of how you could use genetic information to study a category of neuron.
9. What is myelin? What does it do? Which cells provide it in the central nervous system?

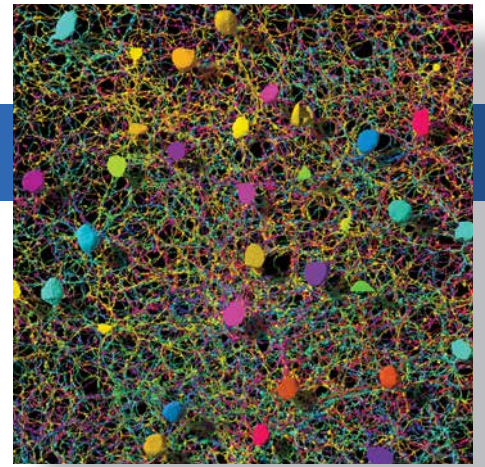


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CHAPTER THREE

The Neuronal Membrane at Rest



INTRODUCTION

THE CAST OF CHEMICALS

Cytosol and Extracellular Fluid

Water

Ions

The Phospholipid Membrane

Protein

Protein Structure

Channel Proteins

Ion Pumps

THE MOVEMENT OF IONS

Diffusion

BOX 3.1 BRAIN FOOD: *A Review of Moles and Molarity*

Electricity

THE IONIC BASIS OF THE RESTING MEMBRANE POTENTIAL

Equilibrium Potentials

BOX 3.2 BRAIN FOOD: *The Nernst Equation*

The Distribution of Ions Across the Membrane

Relative Ion Permeabilities of the Membrane at Rest

BOX 3.3 BRAIN FOOD: *The Goldman Equation*

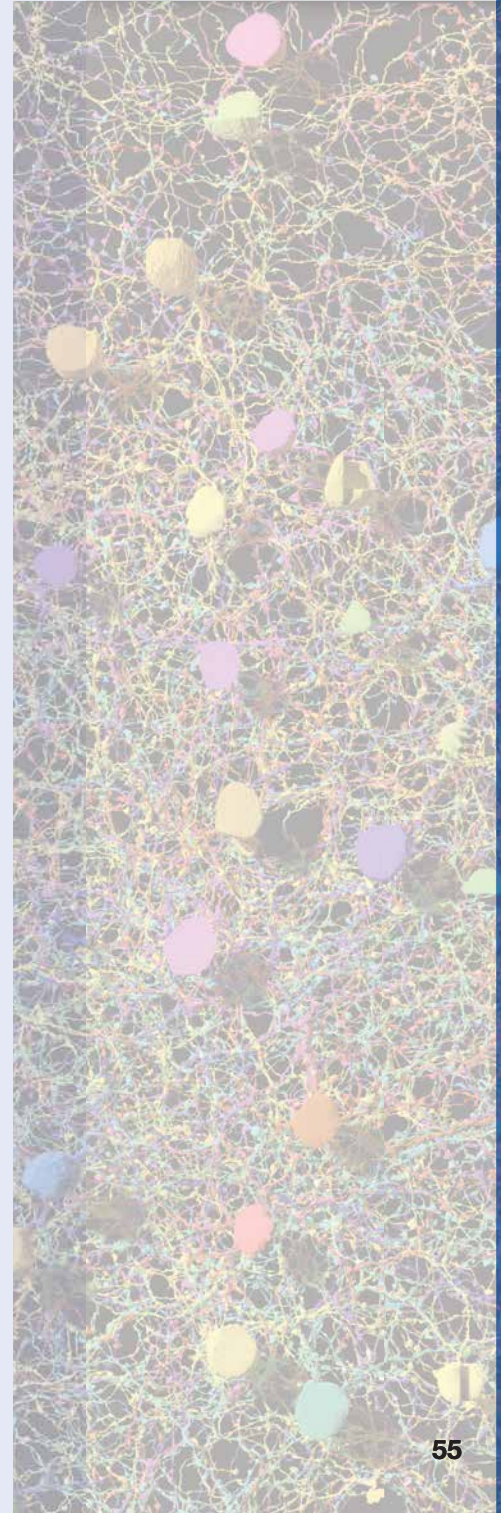
The Wide World of Potassium Channels

BOX 3.4 PATH OF DISCOVERY: *Feeling Around Inside Ion Channels in the Dark,*
by Chris Miller

The Importance of Regulating the External Potassium Concentration

BOX 3.5 OF SPECIAL INTEREST: *Death by Lethal Injection*

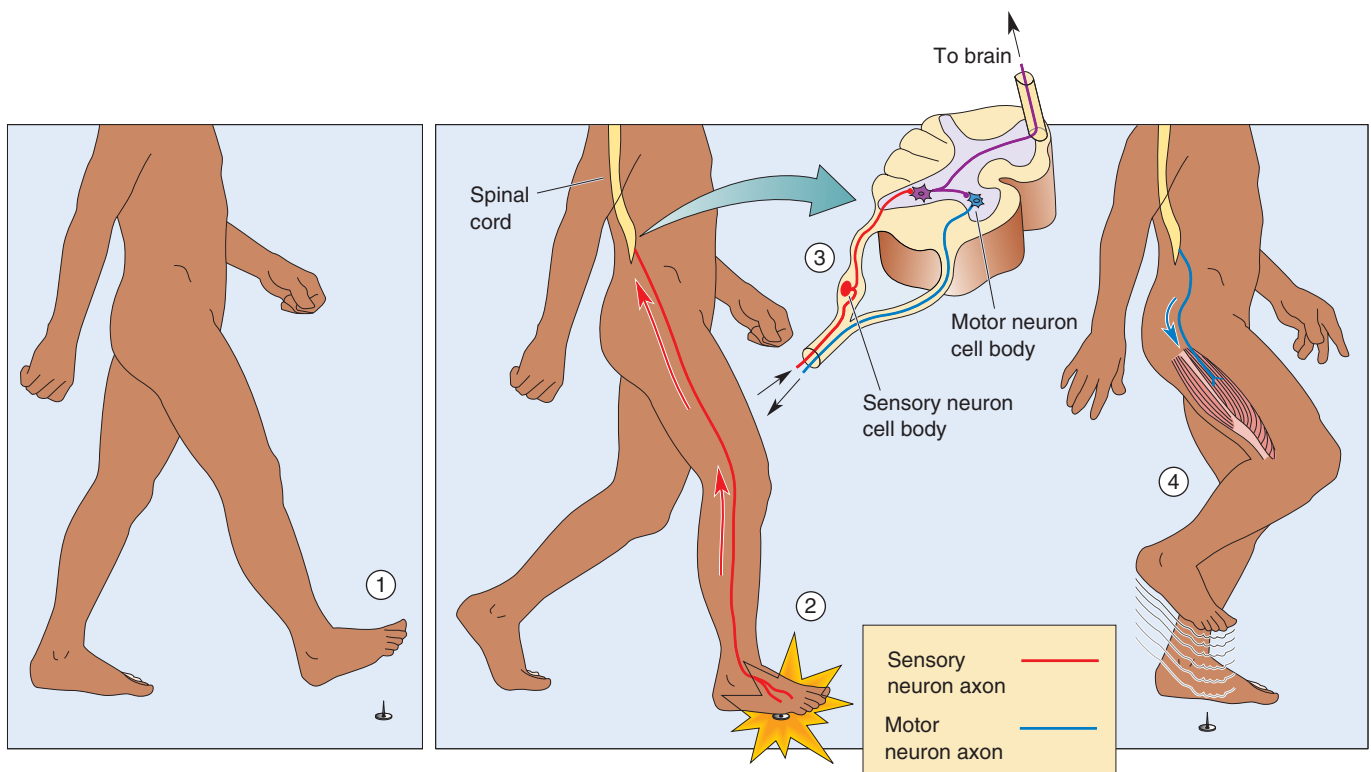
CONCLUDING REMARKS



INTRODUCTION

Consider the problem your nervous system confronts when you step on a thumbtack. Your reactions are automatic: You shriek with pain as you jerk up your foot. For this simple response to occur, breaking of the skin by the tack must be translated into neural signals that travel rapidly and reliably up the long sensory nerves of your leg. In the spinal cord, these signals are transferred to interneurons. Some of these neurons connect with the parts of your brain that interpret the signals as being painful. Others connect to the motor neurons that control the leg muscles that withdraw your foot. Thus, even this simple reflex, depicted in Figure 3.1, requires the nervous system to *collect*, *distribute*, and *integrate* information. A goal of cellular neurophysiology is to understand the biological mechanisms that underlie these functions.

The neuron solves the problem of conducting information over a distance by using electrical signals that sweep along the axon. In this sense, axons act like telephone wires. The analogy stops there, however, because the type of signal used by the neuron is constrained by the special environment of the nervous system. In a copper telephone wire, information can be transferred over long distances at a high rate (about half the speed of light) because telephone wire is a superb conductor of electrons, is well insulated, and is suspended in air (air being a poor conductor of



▲ **FIGURE 3.1**

A simple reflex. ① A person steps on a thumbtack. ② The breaking of the skin is translated into signals that travel up sensory nerve fibers (the direction of information flow, indicated by the arrows). ③ In the spinal cord, the information is distributed to interneurons. Some of these neurons send axons to the brain where the painful sensation is registered. Others synapse on motor neurons, which send descending signals to the muscles. ④ The motor commands lead to muscle contraction and withdrawal of the foot.

electricity). Electrons will, therefore, move within the wire instead of radiating away. In contrast, electrical charge in the cytosol of the axon is carried by electrically charged atoms (ions) instead of free electrons. This makes cytosol far less conductive than copper wire. Also, the axon is not especially well insulated and is bathed in salty extracellular fluid, which conducts electricity. Thus, like water flowing down a leaky garden hose, electrical current flowing down the axon would not go very far before it would leak out.

Fortunately, the axonal membrane has properties that enable it to conduct a special type of signal—the nerve impulse, or **action potential**—that overcomes these biological constraints. As we will see in a moment, the term “potential” refers to the separation of electrical charge across the membrane. In contrast to passively conducted electrical signals, action potentials do not diminish over distance; they are signals of fixed size and duration. Information is encoded in the frequency of action potentials of individual neurons as well as in the distribution and number of neurons firing action potentials in a given nerve. This type of code is somewhat like Morse code sent down an old fashioned telegraph wire; information is encoded in the pattern of electrical impulses. Cells capable of generating and conducting action potentials, which include both nerve and muscle cells, are said to have **excitable membrane**. The “action” in action potentials occurs at the cell membrane.

When a cell with excitable membrane is not generating impulses, it is said to be at rest. In the resting neuron, the cytosol along the inside surface of the membrane has a negative electrical charge compared to the outside. This difference in electrical charge across the membrane is called the **resting membrane potential** (or resting potential). The action potential is simply a brief reversal of this condition, and for an instant—about a thousandth of a second—the inside of the membrane becomes positively charged relative to the outside. Therefore, to understand how neurons signal one another, we must learn how the neuronal membrane at rest separates electrical charge, how electrical charge can be rapidly redistributed across the membrane during the action potential, and how the impulse can propagate reliably along the axon.

In this chapter, we begin our exploration of neuronal signaling by tackling the first question: How does the resting membrane potential arise? Understanding the resting potential is very important because it forms the foundation for understanding the rest of neuronal physiology. And knowledge of neuronal physiology is central to understanding the capabilities and limitations of brain function.

THE CAST OF CHEMICALS

We begin our discussion of the resting membrane potential by introducing the three main players: the salty fluids on either side of the membrane, the membrane itself, and the proteins that span the membrane. Each of these has certain properties that contribute to establishing the resting potential.

Cytosol and Extracellular Fluid

Water is the main ingredient of both the fluid inside the neuron, the intracellular fluid or cytosol, and the outside fluid that bathes the neuron, the extracellular fluid. Electrically charged atoms—ions—that are dissolved in this water are responsible for the resting and action potentials.