PRINCIPLES OF NEUROBIOLOGY

SECOND EDITION

LIQUN LUO

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CRC Press
Taylor & Francis Group
A GARLAND SCIENCE BOOK

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Second edition published 2021
by CRC Press
6000 Broken Sound Parkway NW, Suite 300, Boca Raton, FL 33487-2742
and by CRC Press
2 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN

First edition published by Garland Science (Taylor & Francis Group, LLC) 2016
CRC Press is an imprint of Taylor & Francis Group, LLC

Library of Congress Cataloging-in-Publication Data
Names: Luo, Liqun, 1966– author.
Title: Principles of neurobiology / Liqun Luo.
Description: Second edition. | Boca Raton : Garland Science, 2020. | Includes bibliographical references and index. | Summary: "Principles of Neurobiology, Second Edition presents the major concepts of neuroscience with an emphasis on how we know what we know. The text is organized around a series of key experiments to illustrate how scientific progress is made and helps upper-level undergraduate and graduate students discover the relevant primary literature. Written by a single author in a clear and consistent writing style, each topic builds in complexity from electrophysiology to molecular genetics to systems level in a highly integrative approach. Students can fully engage with the content via thematically linked chapters and will be able to read the book in its entirety in a semester-long course. Principles of Neurobiology is accompanied by a rich package of online student and instructor resources including animations, figures in PowerPoint, and a Question Bank for adopting instructors"— Provided by publisher.
Identifiers: LCCN 2020023964 (print) | LCCN 2020023965 (ebook) | ISBN 9780815346050 (paperback) | ISBN 9780367514716 (hardback) | ISBN 9781003053972 (ebook)
Subjects: LCSH: Neurobiology.
Classification: LCC QP355.2 .L86 2020 (print) | LCC QP355.2 (ebook) | DDC 612.8—dc23
LC record available at https://lccn.loc.gov/2020023964
LC ebook record available at https://lccn.loc.gov/2020023965

ISBN: 9780367514716 (hbk)
ISBN: 9780815346050 (pbk)
ISBN: 9781003053972 (ebk)

Typeset in Utopia Std and Avenir LT Std
by Carol Pierson, Chernow Editorial Services, Inc.

Visit the companion website: www.crcpress.com/cw/luo

To Lubert Stryer—my mentor, colleague, and dear friend.


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PREFACE
TO THE SECOND EDITION

Neurobiology has witnessed rapid advances in the past five years, thanks in part to the support from the U.S. National Institutes of Health's BRAIN Initiative and similar initiatives internationally. To give a few examples: deciphering single-cell transcriptomes across the nervous system has produced valuable information regarding the development and function of specific cell types and has shed light on what constitutes a cell type in complex brain regions. Technological advances in neural circuit dissection, from genetics to anatomy and neurophysiology, have enabled better understanding of many neurobiological processes, from sensation of internal organs to the organization of memory systems in the brain. Breakthrough nucleic acid–based therapies have enabled treatment of devastating neurodegenerative disorders.

The second edition of *Principles of Neurobiology* intends to capture these and many other new advances while maintaining its discovery–based approach: to teach students how knowledge is obtained. This new edition has also added or strengthened many features, thanks to feedback from students and instructors around the globe who have used the first edition in their courses. Major changes include:

- New sections on theory and modeling in Chapter 14 to reflect an increasingly important role theory and modeling play in modern neurobiology. These new sections encompass a wide range of topics from neuronal encoding and decoding to neural circuit architectures and learning algorithms, further expanding the horizon of students of neurobiology.
- Expanded coverage of motor and regulatory systems in separate chapters. The new motor systems chapter has more in-depth discussions of brainstem, cerebellum, basal ganglia, and parietal and frontal cortex in motor coordination, planning, and sensorimotor integration. The new regulatory systems chapter includes new advances on the interoceptive system and the links between homeostatic need and motivated behavior.
- Open questions at the end of each chapter to stimulate students and researchers to explore new terrains.

I would also take this opportunity to highlight several features for students and instructors:

- The current sequence of chapters reflects the course I have been teaching at Stanford, but no single linear sequence can capture the rich interconnections in neurobiology. Embedded in each chapter are many references to other sections and chapters to enable students to make such links. In the electronic version of the textbook, such connections are just one click away.
- Subsets of chapters can be reorganized to cover a variety of courses. For example, Chapters 5, 7, and 11 can be used for a *developmental neurobiology* course. Relevant sections in Chapter 4, 6, 8, 9, 10, and 11 can be used for a *systems neurobiology* course. Both courses can benefit from the basic foundations in Chapters 1–3, the disease connections in Chapter 12, and the evolutionary perspective in Chapter 13. Students can benefit from connections with the rest of the neurobiology. Finally, relevant sections of the entire textbook can be used in a *molecular and cellular neurobiology* course.
- Chapter 14 contains systematic descriptions of major techniques used in neurobiology, from molecular genetics to circuit and behavioral analyses,

and now theory and modeling, and are frequently referred to throughout the text. Students should study the relevant sections in Chapter 14 as often as needed to enhance their understanding of earlier chapters.
- Material in "Boxes" are just as important as the main text. Boxes are created so important materials can be discussed in more depth, with additional examples, or from a different perspective, without interrupting the storylines of the main text.
- Students interested in finding out more about how discoveries are made are highly encouraged to study the primary literature on subjects of interest. These are cited in the figure legends and in "Further Reading" at the end of each chapter (often complementary).

I would like to extend my gratitude to numerous students and instructors who have used first edition of *Principles of Neurobiology* for their feedback and encouragement. I thank the previous Garland Science team, in particular Denise Schanck, for encouraging me to work on this new edition. I am grateful to Chuck Crumly, my editor from CRC Press, whose unwavering support and sage advice have guided me throughout the journey. I am continually indebted to Nigel Orme, whose expert illustrations have made the textbook vivid; working with Nigel on the figures added much fun. I thank many colleagues (see the Acknowledgments) for their expert review and critiques. I owe much gratitude to my PhD student Andrew Shuster, who carefully edited the entire textbook and substantially improved its clarity and accuracy. I thank Jordan Wearing, whose remarkable organization skills and attention to details have enabled smooth transition from manuscripts to final production. I also thank Barbara Chernow and her team for the superb production of the final pages. Finally, I am very grateful to the continuous support of my wife, Charlene Liao, and our two daughters, Connie and Jessica.

Liqun Luo
April 2020

PREFACE
TO THE FIRST EDITION

Neurobiology has never seen a more exciting time. As the most complex organ of our body, the brain endows us the ability to sense, think, remember, and act. Thanks to the conceptual and technical advances in recent years, the pace of discovery in neurobiology is continuously accelerating. New and exciting findings are reported every month. Traditional boundaries between molecular, cellular, systems, and behavioral neurobiology have been broken. The integration of developmental and functional studies of the nervous system has never been stronger. Physical scientists and engineers increasingly contribute to fundamental discoveries in neurobiology. Yet we are still far from a satisfying understanding of how the brain works, and from converting this understanding into effective treatment of brain disorders. I hope to convey the excitement of neurobiology to students, to lay the foundation for their appreciation of this discipline, and to inspire them to make exciting new discoveries in the coming decades.

This book is a reflection of my teaching at Stanford during the past 18 years. My students—and the intended audience of this book—include upper division undergraduates and beginning graduate students who wish to acquire an in-depth knowledge and command of neurobiology. While most students reading this book may have a biology background, some may come from physical sciences and engineering. I have discovered that regardless of a student's background, it is much more effective—and much more interesting—to teach students how knowledge has been obtained than the current state of knowledge. That is why I have taken this discovery-based teaching approach from lecture hall to textbook.

Each chapter follows a main storyline or several sequential storylines. These storylines are divided by large section headings usually titled with questions that are then answered by a series of summarizing subheadings with explanatory text and figures. Key terms are highlighted in bold and are further explained in an expanded glossary. The text is organized around a series of key original experiments, from classic to modern, to illustrate how we have arrived at our current state of understanding. The majority of the figures are based on those from original papers, thereby introducing students to the primary literature. Instead of just covering the vast number of facts that make up neurobiology in this day and age, this book concentrates on the in-depth study of a subset of carefully chosen topics that illustrate the discovery process and resulting principles. The selected topics span the entire spectrum of neurobiology, from molecular and cellular to systems and behavioral. Given the relatively small size of the book, students will be able to study much or all of the book in a semester, allowing them to gain a broad grasp of modern neurobiology.

This book intentionally breaks from the traditional division of neuroscience into molecular, cellular, systems, and developmental sections. Instead, most chapters integrate these approaches. For example, the chapter on 'Vision' starts with a human psychophysics experiment demonstrating that our rod photoreceptors can detect a single photon, as well as a physiology experiment showing the electrical response of the rod to a single photon. Subsequent topics include molecular events in photoreceptors, cellular and circuit properties of the retina and the visual cortex, and systems approaches to understanding visual perception. Likewise, 'Memory, Learning, and Synaptic Plasticity' integrates molecular, cellular, circuit, systems, behavioral, and theoretical approaches with the common goal of understanding what memory is and how it relates to synaptic plasticity. The two chapters on development intertwine with three chapters on sensory and motor systems to help students appreciate the rich connections between the development and function of the nervous system. All chapters are further linked by abundant cross-referencing through the text. These links reinforce the notion

that topics in neurobiology form highly interconnected networks rather than a linear sequence. Finally and importantly, Chapter 13 ('Ways of Exploring') is dedicated to key methods in neurobiology research and is extensively referenced in all preceding chapters. Students are encouraged to study the relevant methods in Chapter 13 when they first encounter them in Chapters 1–12.

This book would not have been possible without the help of Lubert Stryer, my mentor, colleague, and dear friend. From inception to completion, Lubert has provided invaluable support and advice. He has read every single chapter (often more than once) and has always provided a balanced dose of encouragement and criticism, from strategic planning to word choice. Lubert's classic *Biochemistry* textbook was a highlight in my own undergraduate education and has continued to inspire me throughout this project.

I thank Howard Schulman, Kang Shen, and Tom Clandinin, who, along with Lubert, have been my co-instructors for neurobiology courses at Stanford and from whom I have learned a tremendous amount about science and teaching. Students in my classes have offered valuable feedback that has improved my teaching and has been incorporated into the book. I am highly appreciative of the past and current members of my lab, who have taught me more than I have taught them and whose discoveries have been constant sources of inspiration and joy. I gratefully acknowledge the National Institutes of Health and the Howard Hughes Medical Institute for generously supporting the research of my lab.

Although this book has a single author, it is truly the product of teamwork with Garland Science. Denise Schanck has provided wise leadership throughout the journey. Janet Foltin in the initial phase and Monica Toledo through most of the project have provided much support and guidance, from obtaining highly informative reviews of early drafts to organizing teaching and learning resources. I am indebted to Kathleen Vickers for expert editing; her attention to detail and demand for clarity have greatly improved my original text. I owe the illustrations to Nigel Orme, whose combined artistic talent and scientific understanding brought to life concepts from the text. Georgina Lucas's expert page layout has seamlessly integrated the text and figures. I also thank Michael Morales for producing the enriching videos, and Adam Sendroff and his staff for reaching out to the readers. Working with Garland has been a wonderful experience, and I thank Bruce Alberts for introducing Garland to me.

Finally, I am very grateful for the support and love from my wife, Charlene Liao, and our two daughters, Connie and Jessica. Writing this textbook has consumed a large portion of my time in the past few years; indeed, the textbook has been a significant part of our family life and has been a frequent topic of dinner table conversation. Jessica has been my frequent sounding board for new ideas and storylines, and I am glad that she has not minded an extra dose of neurobiology on top of her demanding high-school courses and extracurricular activities.

I welcome feedback and critiques from students and readers!

Liqun Luo
April 2015

NOTE ON GENE AND PROTEIN NOMENCLATURE

This book mostly follows the unified convention of *Molecular Biology of the Cell* 6th Edition by Alberts et al. (Garland Science, 2015) for naming genes. Regardless of species, gene names and their abbreviations are all in italics, with the first letter in upper case and the rest of the letters in lower case. All protein names are in roman, and their cases follow the consensus in the literature. Proteins identified by biochemical means are usually all in lower case; proteins identified by genetic means or by homology with other genes usually have the first letter in upper case; protein acronyms usually are all in upper case. The space that separates a letter and a number in full names includes a hyphen, and in abbreviated names is omitted entirely.

The table below summarizes the official conventions for individual species and the unified conventions that we shall use in this book.

Organism	Species-Specifc Con vention		Unifed Con vention Used in this Book	
	Gene	Protein	Gene	Protein
Mouse	*Syt1*	synaptotagmin I	*Syt1*	Synaptotagmin-1
	Mecp2	MeCP2	*Mecp2*	MeCP2
Human	*MECP2*	MeCP2	*Mecp2*	MeCP2
Caenorhabditis	*unc-6*	UNC-6	*Unc6*	Unc6
Drosophila	*sevenless* (named after recessive phenotype)	Sevenless	*Sevenless*	Sevenless
	Notch (named after dominant mutant phenotype)	Notch	*Notch*	Notch
Other organisms (e.g. jellyfish)		Green fluorescent protein (GFP)	*Gfp*	GFP

RESOURCES FOR INSTRUCTORS AND STUDENTS

The teaching and learning resources for instructors and students are available online. We hope these resources will enhance student learning and make it easier for instructors to prepare dynamic lectures and activities for the classroom.

Instructor Resources

Instructor Resources are available on the Instructor Resources Download Hub, located at www.routledgetextbooks.com/textbooks/instructor_downloads/. These resources are password-protected and available only to instructors adopting the book.

Art of Principles of Neurobiology
All figures from the book are available in two convenient formats: PowerPoint® and PDF. They have been optimized for display on a computer.

Figure-Integrated Lecture Outlines
The section headings, concept headings, and figures from the text have been integrated into PowerPoint presentations. These will be useful for instructors who would like a head start creating lectures for their course. Like all of our PowerPoint presentations, the lecture outlines can be customized. For example, the content of

these presentations can be combined with videos and questions from the book or Question Bank, in order to create unique lectures that facilitate interactive learning.

Animations and Videos
All animations and videos that are available to students are also available to instructors. They can be downloaded from the Instructor Hub in MP4 format. The movies are related to specific chapters, and callouts to the movies are highlighted in green throughout the textbook.

Question Bank
Written by Elizabeth Marin (University of Cambridge), and Melissa Coleman (Claremont McKenna, Pitzer, and Scripps Colleges), the Question Bank includes a variety of question formats: multiple choice, fill-in-the-blank, true-false, matching, essay, and challenging 'thought' questions. There are approximately 40–50 questions per chapter, and a large number of the multiple-choice questions will be suitable for use with personal response systems (that is, clickers). The Question Bank provides a comprehensive sampling of questions that require the student to reflect upon and integrate information, and can be used either directly or as inspiration for instructors to write their own test questions.

Student Resources

Resources for students are available on the books Companion Website, located at www.crcpress.com/cw/luo.

Art of Principles of Neurobiology
All figures from the book are available in two convenient formats: PowerPoint® and PDF. They have been optimized for display on a computer.

Animations and Videos
There are over 40 narrated movies, covering a range of neurobiology topics, which review key concepts and illuminate the experimental process.

Flashcards
Each chapter contains flashcards, built into the student website, that allow students to review key terms from the text.

Glossary
The comprehensive glossary of key terms from the book is online.

Blog
A blog associated with Principles of Neurobiology companion website has monthly new entries, which introduce students to the latest discoveries in research and extend the concepts discussed in the textbook.

ADDITIONAL NOTES ON HOW TO USE THIS BOOK

- Key terms in the text are highlighted in bold font, with glossary entries.
- Extensive cross-references of sections and figures help strengthen the connections between different parts of neurobiology. In the e-book, hyperlinks have been created for these cross-references so students can click the link to study a related figure or a section in a different part of the book, and click again to return to the original page.
- Students are particularly encouraged to study the relevant sections in Chapter 14 when referenced in earlier chapters.
- To emphasize the discovery–based approach, most figures have been adapted from the original literature. For simplicity, error bars and statistics have been omitted for most figures. Interested students can find such details by following the citations in figure legends.

ACKNOWLEDGMENTS

The author and publisher of *Principles of Neurobiology* specially thank Andrew Shuster (Stanford University) for editing the entire textbook, and Melissa Coleman (Claremont McKenna, Pitzer and Scripps Colleges) and Lisa Marin (University of Cambridge) for creating the Question Bank.

The author and publisher of *Principles of Neurobiology* gratefully acknowledge the contributions of the following scientists and instructors for their advice and critique in the development of the second edition of this book:

Chapter 1: Eric Knudsen (Stanford University), Doris Tsao (California Institute of Technology).

Chapter 2: Josh Huang (Cold Spring Harbor Laboratory/ Duke University), John Huguenard (Stanford University), Lily Jan (University of California, San Francisco), Yulong Li (Peking University), Kang Shen (Stanford University), Gina Turrigiano (Brandeis University), Nieng Yan (Princeton University).

Chapter 3: Josh Huang (Cold Spring Harbor Laboratory), Lily Jan (University of California, San Francisco), Erik Jorgensen (University of Utah), Yulong Li (Peking University), Kang Shen (Stanford University), Tom Südhof (Stanford University), Rachel Wilson (Harvard University).

Chapter 4: Tom Clandinin (Stanford University), E. J. Chichilnisky (Stanford University), Tirin Moore (Stanford University), Bill Newsome (Stanford University), Massimo Scanzioni (University of California, San Francisco), Lubert Stryer (Stanford University), Doris Tsao (California Institute of Technology), Wei Wei (University of Chicago).

Chapter 5: Tom Clandinin (Stanford University), Marla Feller (University of California, Berkeley), Andy Huberman (Stanford University), Alex Kolodkin (Johns Hopkins University), Susan McConnell (Stanford University), Carla Shatz (Stanford University), Larry Zipursky (University of California, Los Angeles).

Chapter 6: Diana Bautista (University of California, Berkeley), Xiaoke Chen (Stanford University), Xintong Dong (Johns Hopkins University), Xinzhong Dong (Johns Hopkins University), David Ginty (Harvard University), Eric Knudsen (Stanford University), Shan Meltzer (Harvard University), Adi Mizrahi (Hebrew University), John Ngai (University of California, Berkeley), Greg Scherrer (University of North Carolina).

Chapter 7: Yuh-Nung Jan (University of California, San Francisco), Alex Kolodkin (Johns Hopkins University), Susan McConnell (Stanford University), Sergiu Pașca (Stanford University), Larry Zipursky (University of California, Los Angeles).

Chapter 8: Silvia Arber (University of Basel), Rui Costa (Columbia University), Josh Huang (Cold Spring Harbor), Eve Marder (Brandeis University), Krishna Shenoy (Stanford University), Mark Wagner (Stanford University), Kevin Yackle (University of California, San Francisco).

Chapter 9: Will Allen (Harvard University), Xiaoke Chen (Stanford University), Yang Dan (University of California, Berkeley), Steve Liberles (Harvard University), Brad Lowell (Harvard University), Ruslan Medzhitov (Yale University), Louis Ptáček (University of California, San Francisco), Chen Ran (Harvard University), Bill Snider (University of North Carolina).

Chapter 10: Barry Dickson (Howard Hughes Medical Institute Janelia Research Campus), Catherine Dulac (Harvard University), Weizhe Hong (University of California, Los Angeles), Mala Murthy (Princeton University), Nirao Shah (Stanford University).

Chapter 11: Lu Chen (Stanford University), Edvard Moser (Norwegian University of Science and Technology), Roger Nicoll (University of California, San Francisco), Bill Snider (University of North Carolina), Gerry Rubin (Howard Hughes Medical Institute Janelia Research Campus), Mark Schnitzer (Stanford University), Liz Steinberg (Stanford University), Gina Turrigiano (Brandeis University), Ilana Witten (Princeton University).

Chapter 12: Xiaoke Chen (Stanford University), Lief Fenno (Stanford University), Anirvan Ghosh (Unity Biotechnology), Aaron Gitler (Stanford University), Wei-Hsiang Huang (McGill University), Bill Snider (University of North Carolina), Ryan Watts (Denali Therapeutics).

Chapter 13: Tom Clandinin (Stanford University), Chuck Crumly (CRC Press), Ruslan Medzhitov (Yale University), Alex Pollen (University of California, San Francisco), David Stern (Howard Hughes Medical Institute Janelia Research Campus), Lubert Stryer (Stanford University).

Chapter 14: Will Allen (Harvard University), Tom Clandinin (Stanford University), Claire Cui (Google), Shaul Druckmann (Stanford University), Catherine Dulac (Harvard University), Surya Ganguli (Stanford University), Scott Linderman (Stanford University), Ken Miller (Columbia University), Bill Snider (University of North Carolina), Lubert Stryer (Stanford University), Alice Ting (Stanford University), Mark Wagner (Stanford University), Rachel Wilson (Harvard University), Dan Yamins (Stanford University), Zheng Zhang (New York University, Shanghai).

The author and publisher of *Principles of Neurobiology* gratefully acknowledge the contributions of the following scientists and instructors for their advice on and critiques of the first edition of this book:

Will Allen, Silvia Arber, Steve Baccus, Bruce Baker, Ben Barres, Michael Baum, Richard Benton, Peter Bergold, Nic Berns, Tobias Bonhoeffer, Katja Brose, Linda Buck, John Carlson, Sidi Chen, Xiaoke Chen, Tom Clandinin, Melissa Coleman, Yang Dan, Karl Deisseroth, Laura DeNardo Wilke, Claude Desplan, Hongwei Dong, Xinzhong Dong, Serena Dudek, Catherine Dulac, Dave Feldheim, Marla Feller, Guoping Feng, Russ Fernald, Joe Fetcho, Gord Fishell, Hunter Fraser, Sam Gandy, Surya Ganguli, Xiaojing Gao, David Ginty, Lisa Giocomo, Aaron Gitler, Casey Guenthner, Joachim Hallmayer, Craig Heller, Shaul Hestrin, Simon Hippenmeyer, Weizhe Hong, Hadley Wilson Horch, Mark Horowitz, Josh Huang, Wei-Hsiang Huang, Andy Huberman, Steve Hyman, Lily Jan, Yuh-Nung Jan, Patricia Janak, Greg Jefferis, William Joo, David Julius, Haig Keshishian, Eric Knudsen, Alex Kolodkin, Takaki Komiyama, Richard Levine, Yulong Li, Charlene Liao, Jeff Lichtman, Manyuan Long, Chris Lowe, Jan Lui, Rob Malenka, Dev Manoli, Eve Marder, Lisa Marin, Mike McCloskey, Susan McConnell, Emmanuel Mignot, Kazunari Miyamichi, Adi Mizrahi, Bill Mobley, Tim Mosca, Jeremy Nathans, Bill Newsome, Lisa Olson, Karen Parfitt, Josef Parvizi, Ardem Patapoutian, Dmitri Petrov, John Pizzey, Mu-ming Poo, Chris Potter, David Prince, Martin Raff, Geert Ramakers, Jennifer Raymond, Jing Ren, Michael Rosbash, Botond Roska, Ed Ruthazer, Greg Scherrer, Mark Schnitzer, Tom Schwarz, Matthew Scott, Idan Segev, Nirao Shah, Mehrdad Shamloo, Carla Shatz, Kang Shen, Krishna Shenoy, Annemarie Shibata, Alcino Silva, Malathi Srivatsan, Scott Sternson, Chuck Stevens, Tom Südhof, Karel Svoboda, Larry Swanson, Bosiljka Tasic, Karl Wah Keung Tsim, Mark Wagner, Joy Wan, Fan Wang, Xinnan Wang, Eric Warrant, Ryan Watts, Brady Weissbourd, Marius Wernig, Rachel Wilson, Boon-Seng Wong, Daisuke Yamamoto, Jian Yang, Charles Yanofsky, Larry Young, Haiqing Zhao, Weimin Zhong, Huda Zoghbi.

SPECIAL FEATURES

CONTENTS

CHAPTER 1

An Invitation to Neurobiology

The brain is a world consisting of a number of unexplored continents and great stretches of unknown territory.

Santiago Ramón y Cajal

How does the nervous system control behavior? How do we sense the environment? How does the brain create a representation of the world out of the sensations? How much of our brain function and behavior is shaped by our genes, and how much reflects the environment in which we grew up? How is the brain wired up during development? What changes occur in the brain when we learn something new? How have nervous systems evolved? What goes wrong in brain disorders?

We are about to embark on a journey to explore these questions, which have fascinated humanity for thousands of years. Our ability to address these questions *experimentally* has greatly expanded in recent years. What we currently know about the answers to these questions comes mostly from findings made in the past 50 years; in the next 50 years, we will likely learn more about the brain and its control of behavior than in all of prior human history. We are at an exciting time as students of neurobiology, and it is my hope that many readers of this book will be at the forefront of groundbreaking discoveries.

PRELUDE: NATURE AND NURTURE IN BRAIN FUNCTION AND BEHAVIOR

As we begin this journey, let's discuss one of the questions we raised regarding the contributions of genes and environment to our brain function and behavior. We know from experience that both genetic inheritance (**nature**) and environmental factors (**nurture**) make important contributions, but how much does each contribute? How do we begin to tackle such a complex question? In scientific research, asking the right questions is often a critical step toward obtaining the right answers. As evolutionary geneticist Theodosius Dobzhansky put it, "The question about the roles of the genotype and the environment in human development must be posed thus: To what extent are the *differences* observed among people conditioned by the differences of their genotypes and by the differences between the environments in which people were born, grew and were brought up?"

1.1 Human twin studies can reveal the contributions of nature and nurture

Francis Galton first coined the phrase *nature versus nurture* in the nineteenth century. He also introduced a powerful method for studying this conundrum: statistical analysis of human twins. Identical twins (**Figure 1-1**), or **monozygotic twins**, share 100% of their genes in almost all cells, as they are products of the same fertilized egg, or **zygote**. One can compare specific traits among thousands of pairs of identical twins to see how correlated they are within each pair. For example, if we compare the intelligence quotients (IQs)—an estimate of general intelligence—of any two random people in the population, the correlation is 0. (Correlation is a statistic of resemblance that ranges from 0, indicating no resemblance, to 1, indicating perfect resemblance.) This correlation is 0.86 for identical twins (**Figure 1-2**), a striking similarity. However, identical twins also usually grow

Figure 1-1 Identical (monozygotic) twins. Identical twins develop from a single fertilized egg and therefore share 100% of their genes in almost all cells (some lymphocytes are an exception due to stochasticity in DNA recombination). Most identical twins also share similar childhood environments. (Courtesy of Christopher J. Potter.)

up in the same environment, so this correlation alone does not help us distinguish between the contributions of genes and the environment.

Fortunately, human populations provide a second group that allows researchers to tease apart the influence of genetic and environmental factors. Nonidentical (fraternal) twins occur more often than identical twins in most human populations. These are called **dizygotic twins** because they originate from two independent eggs fertilized by two independent sperm. As full siblings, dizygotic twins are 50% identical in their genes according to Mendel's laws of inheritance. However, like monozygotic twins, dizygotic twins usually share very similar prenatal and postnatal environments. Thus, the differences between traits exhibited by monozygotic and dizygotic twins should result from the differences in 50% of their genes. In our example, the correlation of IQ scores between dizygotic twins is 0.60 (Figure 1-2).

Behavioral geneticists use the term **heritability** to describe the contribution of genetic differences to trait differences. Heritability is defined as the difference between the correlations of monozygotic and dizygotic twins multiplied by 2 (because the genetic difference is 50% between monozygotic and dizygotic twins). Thus, the heritability of IQ is (0.86 – 0.60) × 2 = 0.52. Roughly speaking, then, genetic differences account for about half of the *variation* in IQ scores within human populations. Traditionally, the non-nature component has been presumed to come from environmental factors. However, "environmental factors" as calculated in twin studies include *all* factors not inherited from the parents' DNA. These include the postnatal environment, which is what we typically think of as nurture, but also prenatal environment, stochasticity in developmental processes, somatic mutations (alterations in DNA sequences in somatic cells after fertilization), and gene expression changes due to **epigenetic modifications**. Epigenetic

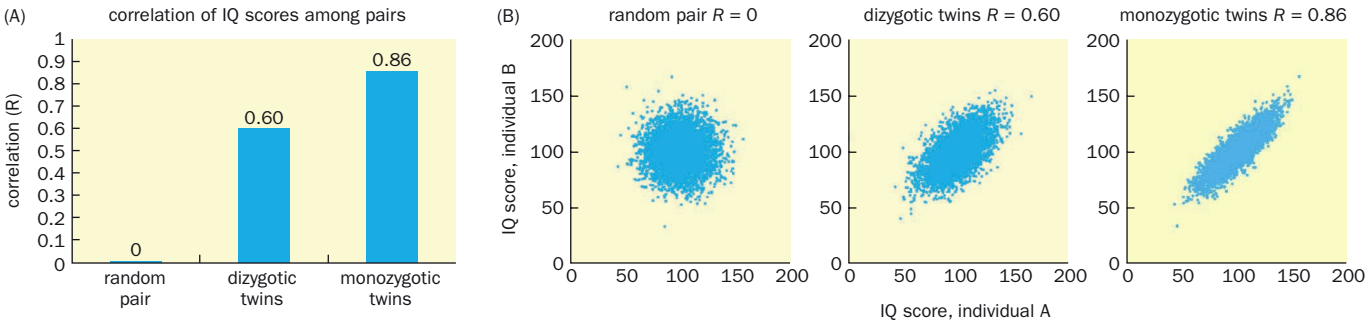

Figure 1-2 Twin studies for determining genetic and environmental contributions to intelligence quotient (IQ). (A) Correlation, or *R* value, of IQ scores for 4672 pairs of monozygotic twins and 5546 pairs of dizygotic twins. The correlation between the IQ scores of randomly selected pairs of individuals is zero. The difference in correlation between monozygotic and dizygotic twins can be used to calculate the heritability of traits. The large sample size makes these estimates highly accurate. **(B)** Simulation of IQ score correlation plots for 5000 pairs of unrelated individuals (*R* = 0), 5000 pairs of dizygotic twins (*R* = 0.60), and 5000 pairs of monozygotic twins (*R* = 0.86). The *x* and *y* axes of a given dot represent the IQ scores of one pair. The simulations assume a normal distribution of IQ scores (mean = 100, standard deviation = 15). (A, based on Bouchard TJ & McGue M [1981] *Science* 212:1055–1059.)

modifications refer to changes made to DNA and chromatin that do not modify DNA sequences but can alter gene expression—these include DNA methylation and various modifications of histones, the protein component of chromatin. As we will learn later, all of these factors contribute to nervous system development, function, and behavior.

Twin studies have been used to estimate the heritability of many human traits, ranging from height (~90%) to the chance of developing schizophrenia (60–80%). An important caveat regarding these estimates is that most human traits result from complex interactions between genes and the environment, and heritability itself can change with the environment. Still, twin studies offer valuable insights into the relative contributions of genes and nongenetic factors to many aspects of brain function and dysfunction in a given environment. The completion of the Human Genome Project and the development of tools permitting detailed examination of the genome sequence data, combined with a long history of medical and psychological studies of human subjects, have made our own species the subject of a growing body of neurobiological research (Section 14.5). However, mechanistic understanding of how genes and the environment influence brain development, function, and behavior requires experimental manipulations that often can be carried out only in animal models. The use of vertebrate and invertebrate model species (Sections 14.1–14.4) has yielded much of what we have learned about the brain and behavior. Many principles of neurobiology revealed by experiments on specific model species have turned out to operate in a wide variety of organisms, including humans.

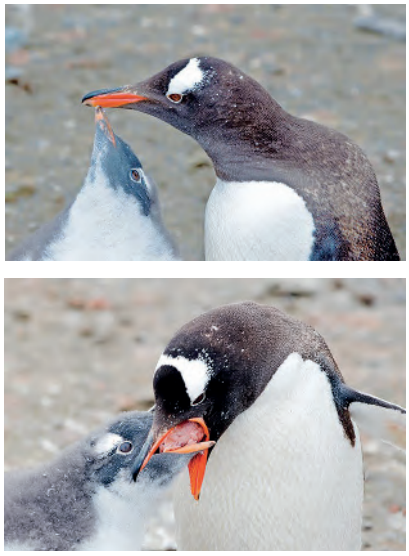

Figure 1-3 Penguin feeding. The instinctive behaviors of an adult penguin and its offspring photographed in Antarctica, 2009. Top, the young penguin asks for food by bumping its beak against its parent's beak. Bottom, the parent releases the food into the young penguin's mouth. (Courtesy of Lubert Stryer.)

1.2 Examples of *nature*: animals exhibit instinctive behaviors

Animals exhibit remarkable instinctive behaviors that help them find food, avoid danger, seek mates, and nurture their progeny. For example, a baby penguin, directed by its food-seeking instinct, bumps its beak against its parent's beak to remind its parent to feed it; in response, the parent instinctively releases the food it has foraged from the sea to feed its baby (**Figure 1-3**).

Instinctive behaviors can be elicited by very specific sensory stimuli. For instance, experimenters have tested the responses of young chicks to an object resembling a bird in flight, with wings placed close to either end of the head–tail axis. When moved in one direction, the object looks like a short-necked, long-tailed hawk; when moved in the other direction, the object looks like a long-necked, short-tailed goose. Seeing the object overhead, a young chick produces different responses depending on the direction in which the object moves, running away when the object resembles a hawk but making no effort to escape when the object resembles a goose (**Figure 1-4**). This escape behavior is **innate**: it is with the chick from birth and is likely genetically programmed. The behavior is also stereotypic: different chicks exhibit the same escape behavior, with similar stimulus specificity. Once the behavior is triggered, it runs to completion without

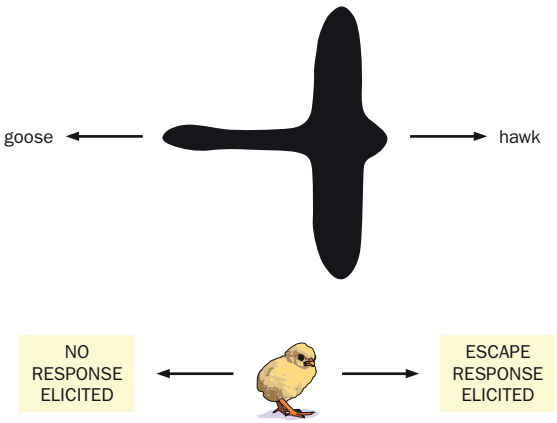

Figure 1-4 Innate escape response of a chick to a hawk. A young chick exhibits instinctive escape behavior in response to an object moving overhead that resembles a short-necked, hawk-like bird; moving the pictured object from left to right triggers this instinctive behavior. Moving the object from right to left so that it resembles a long-necked goose does not elicit the chick's escape behavior. (Adapted from Tinbergen N [1951] The Study of Instinct. Oxford University Press.)

Figure 1-5 Barn owls use their auditory system to locate prey in complete darkness. The photograph was taken in the dark with infrared light flashed periodically while the camera shutter remained open. (Courtesy of Masakazu Konishi.)

further sensory feedback. **Neuroethology**, a field of study that emphasizes observing animal behavior in natural environments, refers to such instinctive behaviors as following **fixed action patterns**. The essential features of the stimulus that activates the fixed action pattern are referred to as **releasers**.

How do genes and developmental programs specify such specific instinctive behaviors? In Chapter 10, we will explore this question using sexual behavior as an example. We will learn about how a single gene in the fruit fly named *fruitless* can exert profound control over many aspects of fruit fly mating behavior.

1.3 An example of *nurture*: barn owls adjust their auditory maps to match altered visual maps

Animals also exhibit a remarkable capacity for learning as they adapt to a changing world. We use the ability of barn owls to adjust their auditory maps to changes in their vision to illustrate this capacity.

Barn owls have superb visual and auditory systems that help them catch prey at night when nocturnal rodents are active. In fact, owls can catch prey even in complete darkness (**Figure 1-5**), relying entirely on their auditory system. They can accurately locate the source of sounds made by prey, based on the small difference in the time it takes for a sound to reach their left and right ears. The owl's brain creates a map of space using these time differences, such that activation of individual nerve cells at specific positions in this brain map informs the owl of the physical position of its prey.

Experiments in which prisms were attached over a juvenile barn owl's eyes (**Figure 1-6**A) revealed how the owl responds when its auditory and visual maps provide conflicting information. Normally, the owl's auditory map matches its visual map, such that perceptions of sight and sound direct the owl to the same location (Figure 1-6B). The prisms shift the owl's visual map 23° to the right. The owl rapidly learns to adjust its motor responses to restore its reaching accuracy on visual targets. However, a mismatch occurs between the owl's visual and auditory maps on the first day after the prisms are placed (Figure 1-6C): sight and sound indicate different locations to the owl, causing confusion about the prey's location. The juvenile owl copes with this situation by adjusting its auditory map to

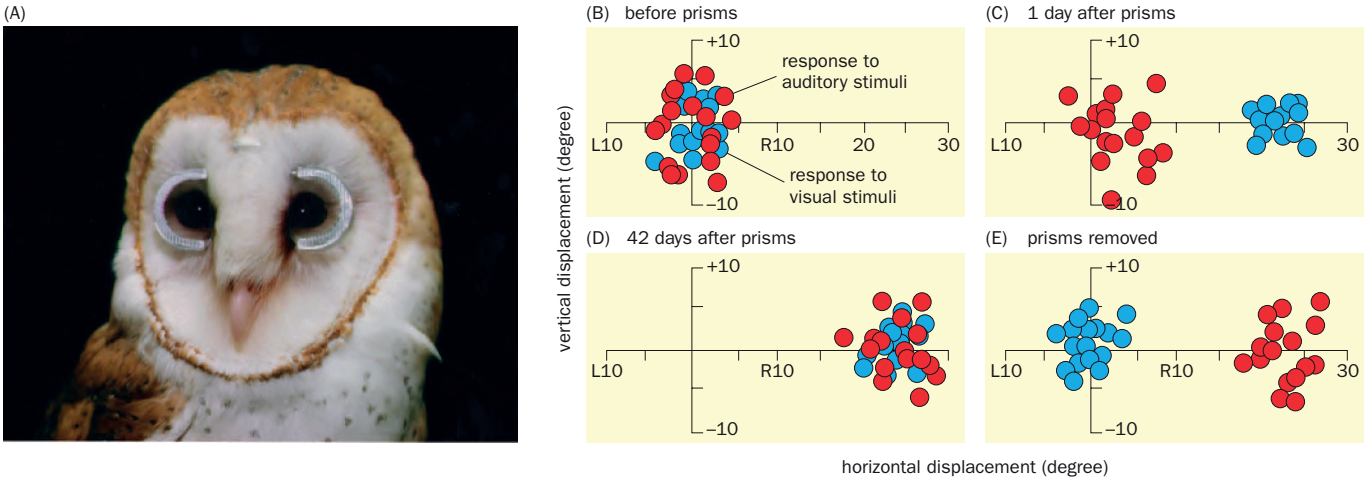

Figure 1-6 Juvenile barn owls adjust their auditory map to match a displaced visual map after wearing prisms. (A) A barn owl fitted with prisms that shift its visual map. **(B)** Before the prisms are attached, the owl's visual map (blue dots) and auditory map (red dots) are matched near 0°. Each dot represents an experimental measurement of an owl's head orientation in response to an auditory or visual stimulus presented in the dark. **(C)** One day after the prisms were fitted, the visual map is displaced 23° to the right of the auditory map. **(D)** After a juvenile owl has worn the prisms for 42 days, its auditory map has adjusted to match its shifted visual map. **(E)** The visual map shifts back immediately after the prisms are removed, causing a temporary mismatch. This mismatch is corrected as the auditory map shifts back soon after (not shown). (A, courtesy of Eric Knudsen. B–E, from Knudsen EI [2002] *Nature* 417:322–328. With permission from Springer Nature.)

match its altered visual map within 42 days after starting to wear the prisms (Figure 1-6D), eliminating the positional conflict between sight and sound. The owl adjusts its strike behavior to accurately target a single location. When the prisms are removed, a mismatch recurs (Figure 1-6E), but the owl adjusts its auditory map and strike behavior back to their native states shortly afterward.

The story of the barn owl is an example of how the nervous system learns to cope with a changing world. Neurobiologists use the term **neural plasticity** to refer to changes in the nervous system in response to experience and learning. But the story does not end here. Studies have shown that plasticity declines with age: juvenile owls have the plasticity required to adjust their auditory map to match a visual map displaced by 23°, but owls will have lost this ability by the time they reach sexual maturity (**Figure 1-7**A). Some human learning capabilities, such as the ability to learn foreign languages, likewise decline with age. Thus, experiments targeted toward improving the plasticity of adult owls may reveal strategies for improving the learning abilities of adult humans as well.

Several ways have been found for adult owls to overcome their limited plasticity in shifting their auditory maps. If an owl experiences adjusting to a 23°-prism shift as a juvenile, it can readily readjust to the same prisms as an adult (Figure 1-7B). Alternatively, even adult owls that cannot adjust to a 23° shift all at once can learn to shift their auditory maps if the visual field displacement is applied in small increments. Thus, by taking baby steps, adult owls can eventually reach nearly the same shift magnitude as young owls. Once they have learned to shift via gradual increments, adult owls can subsequently shift in a single, large step when tested several months after returning to normal conditions (Figure 1-7C).

What are the neurobiological mechanisms underlying these fascinating plasticity phenomena? In Chapters 4 and 6, we will explore the nature of the visual and auditory maps. In Chapters 5 and 7, we will study how neural maps are formed during development and modified by experience. And in Section 11.25, we will address the mechanism of owls' map adjustment in the context of memory and learning. Before studying these topics, however, we need to learn more basics about the brain and its building blocks. We devote the rest of this chapter to providing an overview of the nervous system and introducing how key historical discoveries helped build the conceptual framework of modern neuroscience.

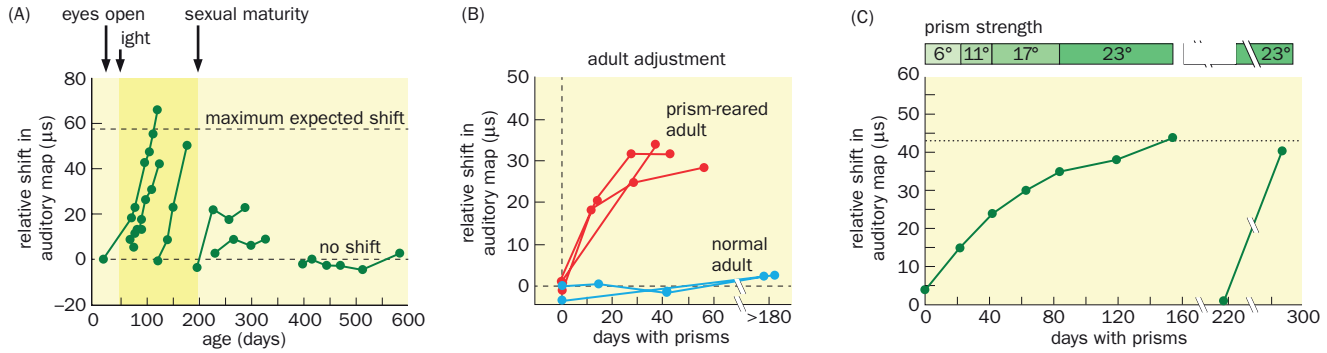

Figure 1-7 Ways to improve the ability of adult barn owls to adjust their auditory maps. (A) Owls' ability to adjust their auditory maps to match displaced visual maps declines with age. The *y* axis quantifies this ability to shift the auditory map, measured by the difference in time (µs, or microseconds) it takes for sounds to reach the left and right ears, which the owl uses to locate objects. Each trace represents a single owl, and each dot represents the average of auditory map shift measured at a specific time after the prisms were applied. The shaded zone indicates a sensitive period, during which owls can easily adjust their auditory maps in response to visual map displacement. Owls older than 200 days have a limited ability to shift their auditory maps. **(B)** Three owls that had learned to adjust their auditory maps in response to prism attachment as juveniles also shifted their auditory maps as adults (red traces). Two owls with no juvenile experience could not shift their maps as adults (blue traces). **(C)** Adult owls could learn to shift their auditory maps if given small prisms in incremental steps, as shown on the left side of the graph. This incremental training enabled adult owls to accommodate a sudden shift to the maximal visual displacement of 23° after a period without prisms, as shown on the right side of the graph. The dotted line at $y = 43$ µs represents the median shift in juvenile owls in response to a single 23°-prism step. (A & B, after Knudsen EI [2002] *Nature* 417:322–328. With permission from Springer Nature. C, after Linkenhoker BA & Knudsen EI [2002] *Nature* 419:293–296. With permission from Springer Nature.)

HOW IS THE NERVOUS SYSTEM ORGANIZED?

For all vertebrate and many invertebrate animals, the nervous system can be divided into the **central nervous system** (**CNS**) and **peripheral nervous system** (**PNS**). The vertebrate CNS consists of the **brain** and the **spinal cord** (**Figure 1-8**A,B). Both structures are bilaterally symmetric; the two sides of the brain are referred as **hemispheres**. The mammalian brain consists of morphologically and

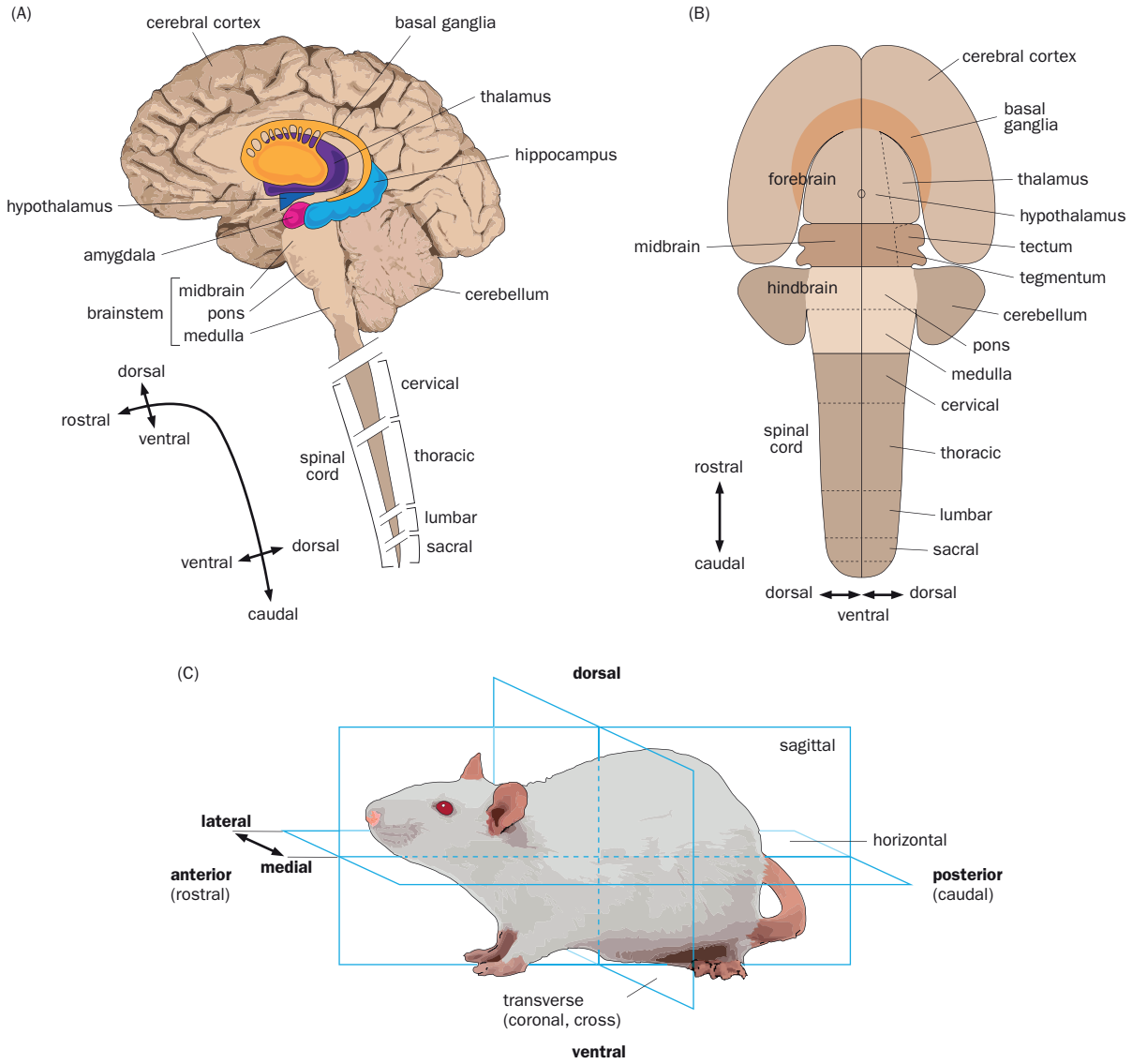

Figure 1–8 The organization of the mammalian central nervous system (CNS). (A) A sagittal (side) view of the human CNS. The basal ganglia (orange), thalamus (purple), hypothalamus (dark blue), hippocampus (light blue), and amygdala (red) from the left hemisphere are superimposed onto a midsagittal section of the CNS (tan background), the left half of which has been cut away to reveal right hemisphere structures (see Panel C for more explanation of the section plane). Major brain structures are indicated and will be studied in greater detail later in the book. From rostral to caudal, the brainstem is divided into midbrain, pons, and medulla. Spinal cord segments are divided into cervical, thoracic, lumbar, and sacral groups. Bottom left, illustration of the rostral–caudal neuraxis (CNS axis). At any given position along the neuraxis in a sagittal plane, the dorsal–ventral axis is perpendicular to the rostral–caudal axis. **(B)** A flatmap of the rat CNS reveals the internal divisions of major brain structures. The flatmap is a two-dimensional representation based on a developmental stage when progenitor cells of the nervous system are arranged as a two-dimensional sheet. It can be approximated by cutting the CNS along the midsagittal plane from the dorsal side and opening the cut surface using the ventral midline as the axis; the ventral-most structures are at the center and the dorsal-most structures are at the sides. (Imagine a book opened to display its pages; the spine of the book—the ventral midline—lays face down.) The left half of the flatmap indicates the major CNS divisions; the right side indicates major subdivisions. **(C)** Schematic illustration of the three principal section planes defined by the body axes. Transverse sections are perpendicular to the rostral–caudal axis, sagittal sections are perpendicular to the medial–lateral axis, and horizontal sections are perpendicular to the dorsal–ventral axis. (B, adapted from Swanson LW [2012] Brain Architecture. 2nd ed. Oxford University Press.)

functionally distinct structures, including the **cerebral cortex**, **basal ganglia**, **hippocampus**, **amygdala**, **thalamus**, **hypothalamus**, **cerebellum**, **midbrain**, **pons**, and **medulla**; the last three structures are collectively called the **brainstem**. The brain can also be divided into **forebrain**, **midbrain**, and **hindbrain**, according to the developmental origins of each region (Figure 7-3A). The spinal cord consists of repeated structures called segments, which are divided into cervical, thoracic, lumbar, and sacral groups. Each segment gives off a pair of spinal nerves. The PNS is made up of **nerves** (discrete bundles of axons) connecting the brainstem and spinal cord with the body and internal organs as well as isolated **ganglia** (clusters of cell bodies of nerve cells) outside the brain and spinal cord. We will study the organization and function of all of these neural structures in subsequent chapters.

The internal structure of the nervous system has traditionally been examined in histological sections. Three types of sections are commonly used and are named following the conventions of histology. In **transverse sections**, also called cross or **coronal sections**, section planes are perpendicular to the long, **anterior–posterior** axis of the animal (also termed the **rostral–caudal** axis, meaning snout to tail). In **sagittal sections**, section planes are perpendicular to the **medial–lateral** axis (midline to side) of the animal. In **horizontal sections**, section planes are perpendicular to the **dorsal–ventral** (back to belly) axis (Figure 1-8C). Note that in humans and other primates, which have a curved CNS, some of the anatomical terms may differ from these definitions. For uniformity, the definition of the rostral–caudal axis in this book always follows the **neuraxis** (axis of the CNS; bottom left of Figure 1-8A) rather than the body axis. Transverse or coronal sections are perpendicular to the neuraxis while horizontal sections are in parallel with the neuraxis. The neuraxis is defined by the curvature of the embryonic **neural tube**, from which the vertebrate nervous system derives, as we will learn in Chapter 7.

1.4 The nervous system consists of neurons and glia

The nervous system is made up two major categories of cells: **neurons** (nerve cells) and **glia**. A typical neuron has two kinds of **neuronal processes** (cytoplasmic extensions): a long, thin process called the **axon**, which often extends far beyond the cell body (**soma**), and thick, bushy processes called **dendrites**, which are usually close to the soma (**Figure 1-9**A). At the ends of the axons are **presynaptic terminals**, specialized structures that participate in the transfer of information between neurons. Dendrites of many vertebrate neurons are decorated with

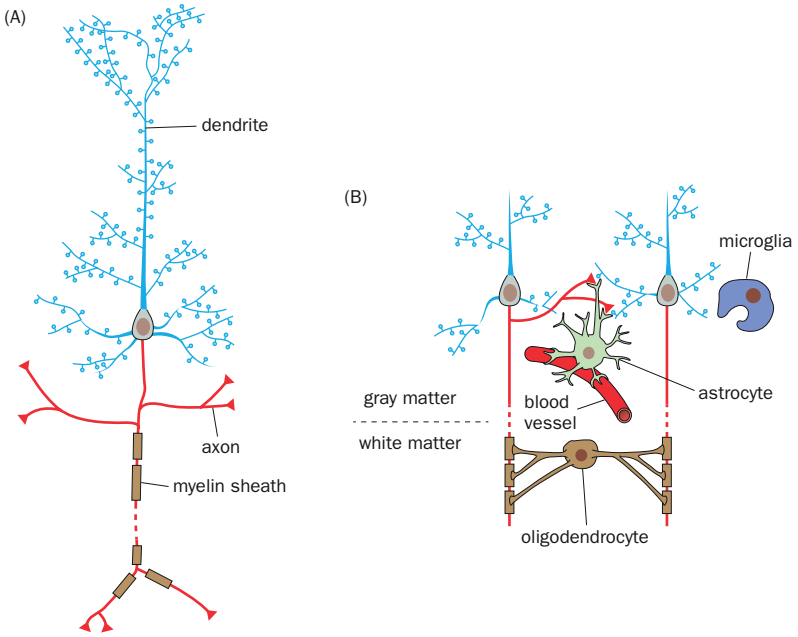

Figure 1-9 Neurons and glia. **(A)** Schematic drawing of a typical neuron in the mammalian CNS. Dendrites are in blue; the axon is in red. The dashed break in the axon indicates that it can extend a long distance from the cell body. The brown structures surrounding the axon are myelin sheaths made by glia. The triangles at the ends of the axonal branches represent presynaptic terminals and the protrusions along the dendritic tree are dendritic spines. **(B)** Schematic drawing of glia in the CNS. Oligodendrocytes form myelin sheaths to wrap the axons of CNS neurons. (Schwann cells, not shown here, play a similar role in the PNS.) Astrocyte end feet wrap around connections between neurons (or synapses, which will be introduced later) in addition to blood vessels. Microglia are immune cells that engulf damaged cells and debris upon activation by injury and during developmental remodeling. (B, based on Allen NJ & Barres BA [2009] *Nature* 457:675–677.)

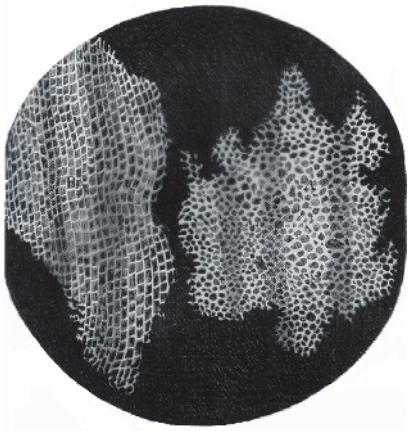

Figure 1-10 The fr st image of cells. A drawing by Robert Hooke illustrates the repeating units visible in thin sections of cork under a primitive microscope. Hooke thought the units resembled small rooms and coined the term *cell*s to describe them. (From Hooke R [1665] Micrographia. J. Martyn and J. Allestry.)

small protrusions called **dendritic spines**, which likewise function in intercellular information transfer. Over the course of this book, we will encounter many neuronal types with distinct morphologies. Most of them have well-differentiated axons and dendrites serving distinct functions, as will be discussed in Section 1.7.

There are four major types of glia in vertebrate nervous systems: **oligodendrocytes**, **Schwann cells**, **astrocytes**, and **microglia** (Figure 1-9B). Oligodendrocytes and Schwann cells play analogous functions in the CNS and PNS, respectively: they wrap axons with their cytoplasmic extensions, called **myelin sheath**, which increases the speed at which information propagates along axons. Oligodendrocytes and myelinated axons constitute **white matter** in the CNS because myelin is rich in lipids and thus appears white. Astrocytes play many roles in neural development and regulation of neuronal communication; they are present in the **gray matter** of the CNS, which is enriched in neuronal cell bodies, dendrites, axon terminals, and connections between neurons. Microglia are the resident immune cells of the nervous system: they engulf damaged cells and debris and help reorganize neuronal connections during development and in response to experience. Invertebrate nervous systems have a similar division of labor for different glial types.

1.5 Individual neurons were first visualized by the Golgi stain in the late nineteenth century

Contemporary students of neurobiology may be surprised to learn that the cellular organization of the nervous system was not uniformly accepted at the beginning of the twentieth century, well after biologists in other fields had embraced the cell as the fundamental unit of life. Robert Hooke first used the term *cell* in 1665 to describe the repeating units he observed in thin slices of cork (**Figure 1-10**) when using a newly invented piece of equipment—the microscope. Scientists subsequently used microscopes to observe many biological samples and found cells to be ubiquitous structures. In 1839, Matthias Schleiden and Theodor Schwann formally proposed the **cell theory**: all living organisms are composed of cells as their basic units. The cell theory was widely accepted in almost every discipline of biology by the second half of the nineteenth century, except among researchers studying the nervous system. Although cell bodies had been observed in nervous tissues, many histologists of that era believed that nerve cells were linked together by their elaborate processes to form a giant net, or reticulum, of nerves. Proponents of this **reticular theory** believed that the reticulum as a whole, rather than its individual cells, constituted the unit of the nervous system.

Among the histologists who supported the reticular theory of the nervous system was Camillo Golgi, who made many important contributions to science, including the discovery of the Golgi apparatus, an intracellular organelle responsible for processing proteins in the secretory pathway (Figure 2-1). Golgi's greatest contribution, however, was the invention of the **Golgi stain**. When a piece of neural tissue is soaked in a solution of silver nitrate and potassium dichromate in the dark for several weeks, black precipitates (microcrystals of silver chromate) stochastically form in a small fraction of nerve cells, rendering these cells visible against an unstained background. Importantly, once black precipitates form within a cell, an autocatalytic reaction occurs such that the entire cell, including most or all of the elaborate extensions, can be visualized in its native tissue (**Figure 1-11**). Golgi stain thus enabled visualization of the entire morphology of individual neurons for the first time. Despite inventing this key method for neuronal visualization, however, Golgi remained a believer in the reticular theory (**Box 1-1**).

It took another great histologist, Santiago Ramón y Cajal, to effectively refute the reticular theory. The work of Ramón y Cajal and several contemporaries instead supported the **neuron doctrine**, which postulated that neuronal processes do not fuse to form a continuous reticulum. Instead, neurons intimately contact each other, with communication between distinct neurons occurring at these contact sites (Box 1-1). The term **synapse** was later coined by Charles

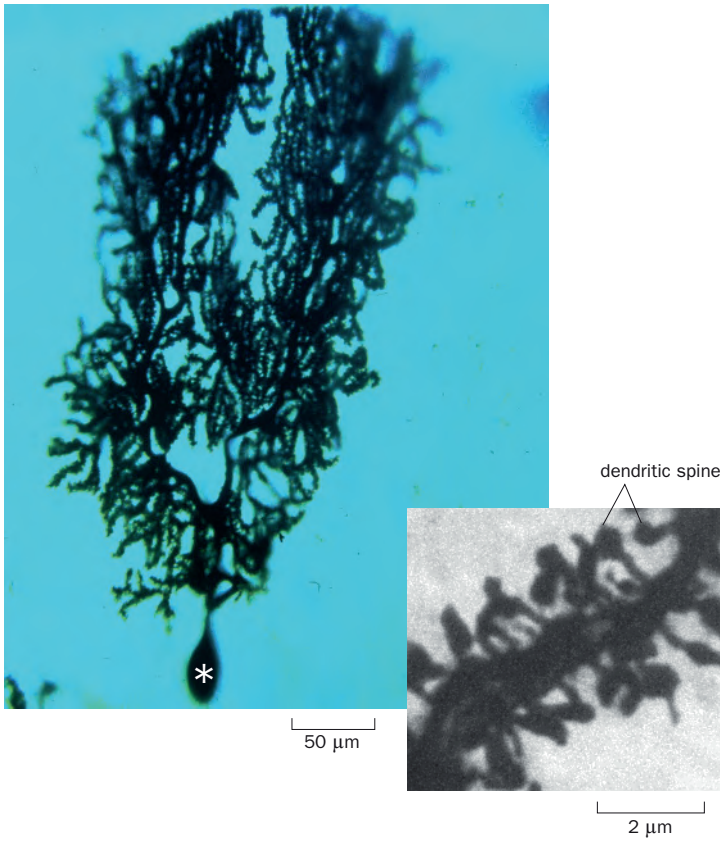

Figure 1-11 Golgi stain. An individual Purkinje cell in the mouse cerebellum is stained black by the formation of silver chromate precipitate, allowing visualization of its complex dendritic tree. The axon, which is not included in this image, projects downward from the cell body indicated by an asterisk. The inset shows a higher magnification of a dendritic segment, highlighting protruding structures called dendritic spines. (Adapted from Luo L, Hensch TK, Ackerman L, et al. [1996] *Nature* 379:837–840. With permission from Springer Nature.)

Sherrington to describe these sites, at which signals flow from one neuron to another. After systematically applying the Golgi stain to study tissues in many parts of the nervous systems of many organisms, ranging from insects to humans, and at many developmental stages, Ramón y Cajal concluded that individual neurons are embryologically, structurally, and functionally independent units of the nervous system.

Box 1-1: The debate between Ramón y Cajal and Golgi: why do scientists make mistakes?

Camillo Golgi and Santiago Ramón y Cajal were the most influential neurobiologists of their time. They shared the 1906 Nobel Prize for Physiology or Medicine, the first to be awarded for findings in the nervous system. However, their debates on how nerve cells constitute the nervous system—via a reticular network or as individual neurons communicating with each other through synaptic contacts—continued during their Nobel lectures (**Figure 1-12**A,B). We now know that Ramón y Cajal's view was correct and Golgi's view was largely incorrect. For example, utilizing the brainbow method (Section 14.18), individual neurons, their dendritic trees, and even their axon terminals can be visualized in and distinguished by distinct colors (Figure 1-12C). Interestingly, Ramón y Cajal used the Golgi stain to refute Golgi's theory. Why didn't Golgi reach the correct conclusion using his own method? Was he not a careful observer? After all, he made many great discoveries, including those describing the Golgi apparatus. According to Ramón y Cajal's analysis, "Golgi arrived at this conclusion by an unusual blend of accurate observations and preconceived ideas. . . . Golgi's work actually consists of two separate parts. On the one hand, there is his method, which has generated a prodigious number of observations that have been enthusiastically confirmed. But on the other, there are his interpretations, which have been questioned and rejected."

Before the invention of the Golgi stain, histologists could not resolve processes of individual nerve cells and therefore believed that nerve processes were fused together in a giant net. Golgi was trained in a scientific environment in which this reticular theory was the dominant interpretation of nervous system organization and so tried to fit his observations into existing theory. For example, even though Golgi was the first to discover, using his staining method, that dendritic

(*Continued*)

Box 1-1: continued

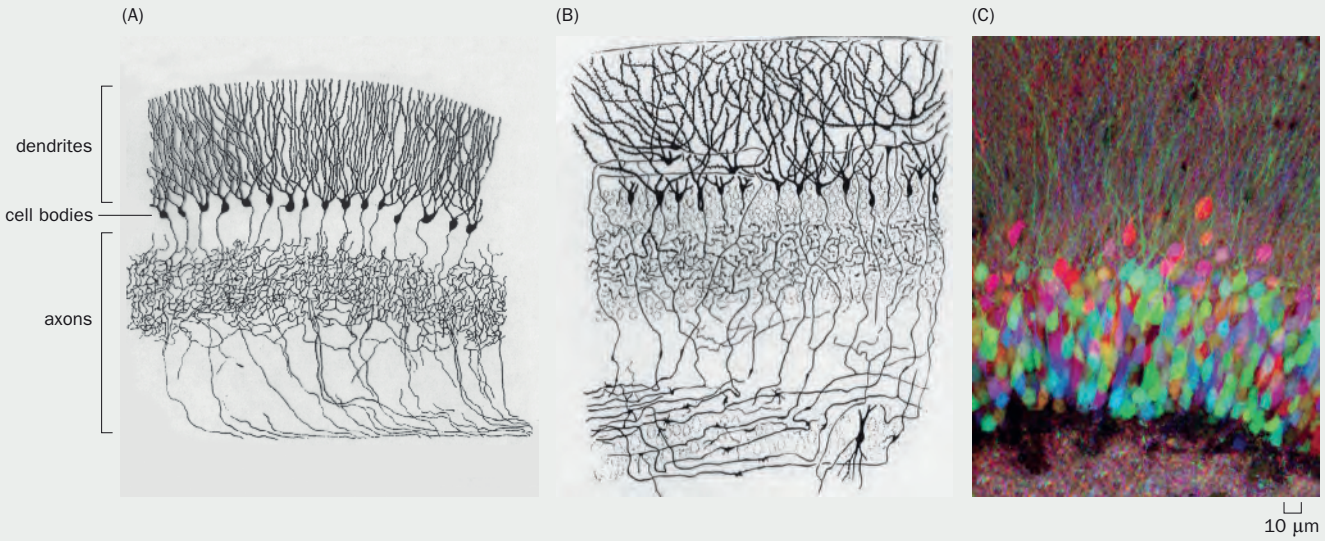

Figure 1-12 Three different views of hippocampal granule cells. **(A)** Golgi's drawing of granule cells of the hippocampus. The dendritic, cell body, and axonal layers are indicated on the left. In Golgi's drawing, all axons are fused together to form a giant reticulum. **(B)** Ramón y Cajal's depiction of the same hippocampal granule cells. Note that axons below the cell bodies have definitive endings. **(C)** Hippocampal granule cells labeled by the brainbow technique, which allows the spectral separation of individual neurons expressing different mixtures of cyan, yellow, and red fluorescent proteins. Not only cell bodies but also some dendrites above and axon terminals below can be resolved by different colors. (A, after Golgi C [1906] Nobel Lecture. B, after Ramón y Cajal S [1911] Histology of the Nervous System of Man and Vertebrates. Oxford University Press. C, after Livet J, Weissman TA, Kang H, et al. [2007] *Nature* 450:56–62. With permission from Springer Nature.)

trees have free endings (Figure 1-12A, top), he thought that dendrites were used to collect nutrients for nerve cells. He believed that it was their axons, which formed an inseparable giant net as he viewed them (Figure 1-12A, bottom), that performed all the special functions of the nervous system. This story teaches an important lesson: scientists need to be observant, but they also need to be as *objective and unbiased* as possible when interpreting their own observations.

1.6 Twentieth-century technology confirmed the neuron doctrine

Ramón y Cajal could not convince Golgi to abandon the reticular theory, but many lines of evidence since the Golgi–Ramón y Cajal debate (Box 1-1) have provided strong support for the neuron doctrine. For example, during development, neurons begin with only cell bodies. Axons then grow out from the cell bodies toward their final destinations. This was demonstrated by observing axon growth *in vitro* via experiments made possible by tissue culture techniques, which were initially developed for the purpose of visualizing neuronal process growth (**Figure 1-13**). Axons are led by a structure called the **growth cone**, which changes its shape dynamically as axons extend. We will learn more about the function of the growth cone in axon guidance in Chapter 5.

The final pieces of evidence that neuronal processes are not fused with each other came from observations made possible by the development of **electron microscopy**, a technique allowing visualization of structures at nanometer (nm) resolution. (Conventional **light microscopy**, which scientists since Hooke have used to observe biological samples, cannot resolve structures less than 200 nm apart because of the physical properties of light.) The use of electron microscopy to examine **chemical synapses** (so named because communication between cells is mediated by release of chemicals called **neurotransmitters**) revealed that the **synaptic cleft**, a 20–100 nm gap, separates a neuron from its target, which can be another neuron or a muscle cell (**Figure 1-14**A). Synaptic partners are not symmetric: presynaptic terminals of neurons contain small **synaptic vesicles** filled

with neurotransmitters, which, upon stimulation, fuse with the plasma membrane and release neurotransmitters into the synaptic cleft. Postsynaptic target cells have **postsynaptic specializations** (also called **postsynaptic densities**) enriched in neurotransmitter receptors on their plasma membrane surfaces. Chemical synapses are the predominant type of synapse allowing neurons to communicate with each other and with muscle cells. We will study them in greater detail in Chapter 3.

Neurons can also communicate with each other by **electrical synapses** mediated by **gap junctions** (Figure 1-14B). Here, each partner neuron contributes protein subunits to form gap junction channels that directly link the cytoplasms of two adjacent neurons, allowing ions and small molecules to travel between them. These gap junctions come closest to what the reticular theory would imagine as a fusion between different neurons. However, macromolecules cannot pass between gap junctions, and the neurons remain distinct cells with highly regulated communication. The existence of gap junctions, therefore, does not violate the premise that *individual neurons are the building blocks of the nervous system*.

1.7 In vertebrate neurons, information generally flows from dendrites to cell bodies to axons

As introduced in Section 1.4, neurons have two kinds of processes: dendrites and axons. The dendritic morphologies and axonal projection patterns of specific types of neurons are characteristic and are often used for classification. For example, the most frequently encountered type of neuron in the mammalian cerebral cortex and hippocampus, the **pyramidal neuron**, has a pyramid-shaped cell body with an apical dendrite and several basal dendrites that branch extensively (**Figure 1-15**A). Much of the dendritic tree sprouts dendritic spines (Figure 1-11 inset), which contain postsynaptic specializations in close contact with presynaptic terminals of partner neurons. Another widely encountered neuronal type, **basket cells** (Figure 1-15B), wrap their axon terminals around the cell bodies of pyramidal cells in the cerebral cortex or **Purkinje cells** (Figure 1-11) in the cerebellum.

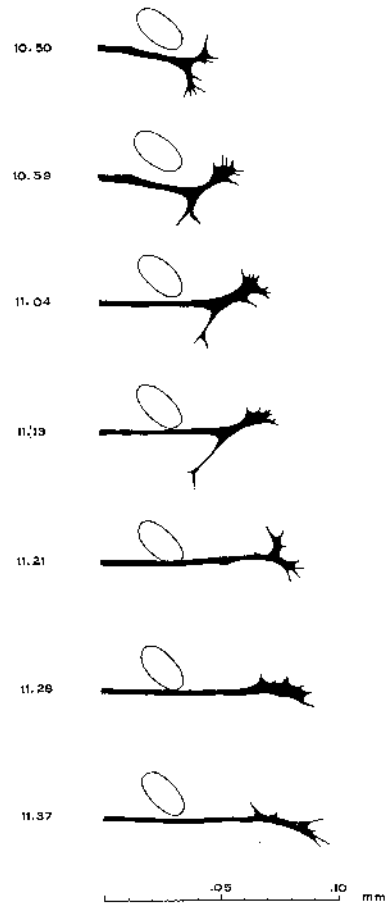

Figure 1-13 The fr st time-lapse depiction of a growing axon. Frog embryonic spinal cord tissue was cultured *in vitro*. Growth of an individual axon was sketched with the aid of a camera lucida at the time indicated on the left (hour.minute). The stationary blood vessel (oval) provided a landmark for the growing tips of the axon, called growth cones, which undergo dynamic changes in shape, including both extensions and retractions. A distance scale is at the bottom of the figure. (From Harrison RG [1910] *J Exp Zool* 9:787–846.)

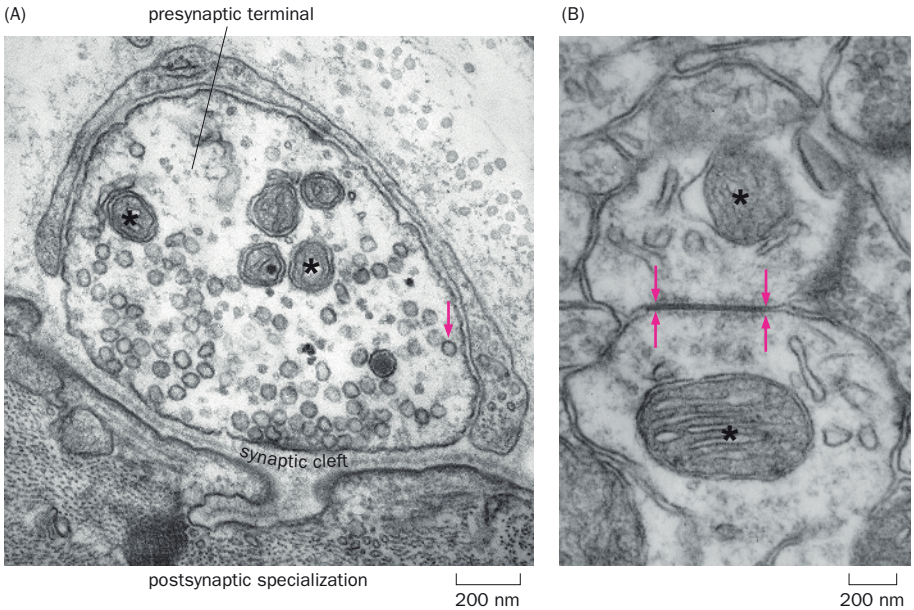

Figure 1-14 Chemical and electrical synapses. (A) Electron micrograph of a chemical synapse between the presynaptic terminal of a motor neuron and the postsynaptic specialization of its target muscle cell. A synaptic cleft separates the two cells. The arrow points to a synaptic vesicle. **(B)** Electron micrograph of an electrical synapse (gap junction) between two dendrites of mouse cerebral cortical neurons. Two opposing pairs of arrows mark the border of the electrical synapse. Asterisks indicate mitochondria in both micrographs. (A, courtesy of Jack McMahan. B, courtesy of Josef Spacek & Kristen M. Harris, SynapseWeb.)

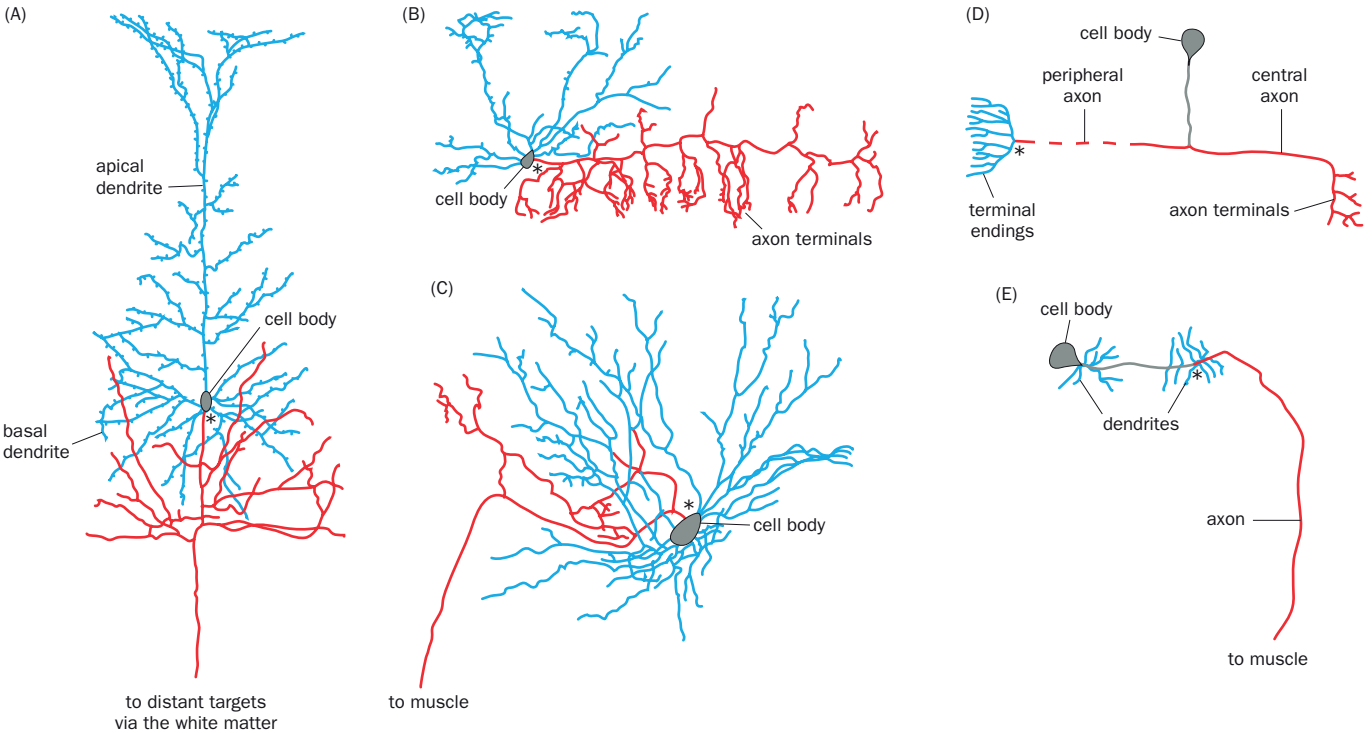

Figure 1-15 Morphological diversity of neurons. (A) A pyramidal cell from rabbit cerebral cortex. A typical pyramidal cell has an apical dendrite (blue) that gives off branches as it ascends, several basal dendrites (blue) that emerge from the cell body, and an axon (red) that branches locally and projects to distant targets. **(B)** A basket cell from mouse cerebellum. The basket cell axon (red) forms a series of "basket" terminals that wrap around Purkinje cell bodies (not drawn). **(C)** A motor neuron from cat spinal cord. Its bushy dendrites (blue) receive input within the spinal cord, and its axon (red) projects outside the spinal cord to muscle, while also leaving behind local branches. **(D)** A mammalian sensory neuron from a dorsal root ganglion. A single process from the cell body bifurcates into a peripheral axon (dashed to indicate the long distance) with terminal endings in the skin (equivalent of dendrites for collecting sensory information) and a central axon that projects into the spinal cord. **(E)** A motor neuron from the fruit fly ventral nerve cord (equivalent to the vertebrate spinal cord). Most invertebrate central neurons are unipolar: a single process extends out of the cell body, giving rise to dendritic branches (blue) and an axon (red). In all panels, asterisks denote axon initiation segments; as will be discussed in Section 1.8, action potentials are usually initiated at these sites. (A–D, adapted from Ramón y Cajal S [1911] Histology of the Nervous System of Man and Vertebrates. Oxford University Press. E, based on Lee T & Luo L [1999] *Neuron* 22:451–461.)

The spinal cord **motor neuron** extends bushy dendrites within the spinal cord (Figure 1-15C) and projects its axon out of the spinal cord and into muscle. Located in the **dorsal root ganglion** just outside the spinal cord, a **sensory neuron** of the **somatosensory system** (which processes bodily sensation) extends a single process that bifurcates, forming a peripheral axon that gives rise to branched terminal endings and a central axon that projects into the spinal cord (Figure 1-15D). Most vertebrate neurons have both dendrites and an axon leaving the cell body, and hence are called **multipolar** (or **bipolar** if there is only a single dendrite); somatosensory neurons are *pseudounipolar* because, although there is just one process leaving the cell body, it gives rise to both peripheral and central branches.

What is the direction of information flow within individual neurons? After systematically observing different types of neurons in various parts of the nervous system, Ramón y Cajal proposed the **theory of dynamic polarization**: transmission of neuronal signals proceeds from dendrites and cell bodies to axons. Therefore, every neuron has (1) a receptive component, the cell body and dendrites; (2) a transmission component, the axon; and (3) an effector component, the axon terminals. With few exceptions (the somatosensory neuron being one), this important principle has been validated by numerous observations and experiments since it was proposed a century ago and has been used extensively to deduce the direction of information flow in the vertebrate CNS. We will study the cell biological basis of neuronal polarization in Chapter 2.

How did observing the morphologies of individual neurons lead to the discovery of this rule? Ramón y Cajal took advantage of the fact that, in sensory systems,

information must generally flow from sensory organs to the brain. By examining different neurons along the visual pathway (**Figure 1-16**), for example, one can see that at each connection, dendrites are at the receiving end, facing the external world, while axons are oriented so as to deliver such information to more central targets, sometimes at a great distance from the cell body where the axon originates. This applies to neurons in other sensory systems as well. Conversely, in motor systems, information must generally flow from the CNS to the periphery. The morphology of the motor neuron indeed supports the notion that its bushy dendrites receive input within the spinal cord, and its long axon, projecting to muscle, provides output (Figure 1-15C).

Neuronal processes in invertebrates can also be defined as dendrites and axons according to their *functions*, with dendrites positioned to receive information and axons to send it. However, the morphological differentiation of most invertebrate axons and dendrites, especially in the CNS, is not as clear-cut as it is for vertebrate neurons. Most often, invertebrate neurons are **unipolar**, extending a single process giving rise to both dendritic and axonal branches (Figure 1-15E). Dendritic branches are often, but not always, closer to the cell body. In many cases, the same branches can both receive and send information; this occurs in some vertebrate neurons as well, as we will learn in Chapters 4 and 6. Thus, in the "simpler" invertebrate nervous systems, it is more difficult to deduce the direction of information flow by examining the morphology of individual neurons.

1.8 Neurons use changes in membrane potential and neurotransmitter release to transmit information

What is the physical basis of information flow *within* neurons? We now know that the nervous system uses electrical signals to propagate information. The first evidence of this came from Luigi Galvani's discovery, in the late eighteenth century, that application of an electric current could generate muscle twitches in frogs. It was known by the beginning of the twentieth century that electrical signals were spread in neurons via transient changes in **membrane potential**, the electrical potential difference across the neuronal membrane. As we will learn in more detail in Chapter 2, neurons at the resting state are more negatively charged inside the cells compared to outside the cells. When neurons are excited, their membrane potentials change transiently, creating **nerve impulses** that propagate along their axons. But how is information relayed through nerve impulses? Quantitative studies of how sensory stimuli of different magnitudes induce nerve impulses provided important clues.

Studies of muscle contraction in response to electrical stimulation of motor nerves suggested that an elementary nerve impulse underlies different stimulus strengths. An all-or-none conduction principle became evident when amplifiers for electrical signals built in the 1920s made it possible to record nerve impulses from single axon fibers in response to sensory stimulation. Edgar Adrian and co-workers systematically measured nerve impulses from somatosensory neurons (Figure 1-15D) that convey information about touch, pressure, and pain to the spinal cord. They found that individual nerve impulses were of a uniform size and shape, whether they were elicited by weak or strong sensory stimuli; stronger stimuli increased the frequency of such impulses but not the properties of each impulse (**Figure 1-17**).

These experiments led to two important concepts in modern neuroscience. The first concept is the presence of an elementary unit of nerve impulses that axons use to convey information across long distances; we now call this elementary unit an **action potential**. In Chapter 2, we will study in greater detail the molecular basis of action potentials, including why they exhibit the all-or-none property. The second concept is that neurons use the frequency of action potentials to convey the intensity of signals. Whereas the frequency of action potentials is the most widely used means to convey signal intensity throughout the nervous system, the timing of action potentials can also convey important information.

In addition to action potentials, another important form of communication within neurons are **graded potentials**—membrane potentials that vary continuously

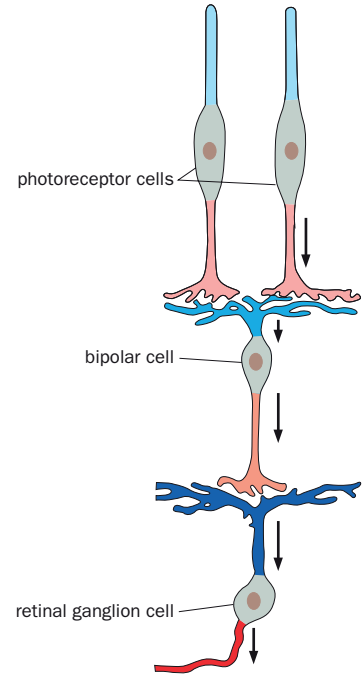

Figure 1–16 Neurons and information fow in the ver tebrate retina. Visual information is collected by photoreceptor cells in the retina, communicated to the bipolar cell, and then to the retinal ganglion cell, which projects a long-distance axon into the brain. Note that for both the bipolar cell and the retinal ganglion cell, information is received by their dendrites (blue) and sent via their axons (red). The photoreceptor processes can also be divided into a dendrite equivalent that detects light (blue) and an axon that sends output to the bipolar cell. Arrows indicate the direction of information flow. We will learn more about these cells and connections in Chapter 4. (Adapted from Ramón y Cajal S [1911] Histology of the Nervous System of Man and Vertebrates. Oxford University Press.)