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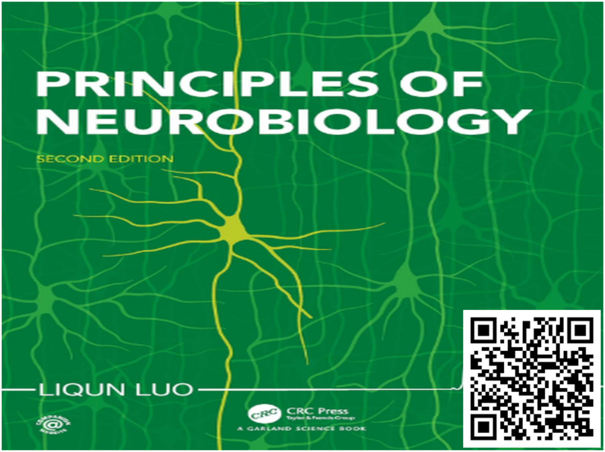

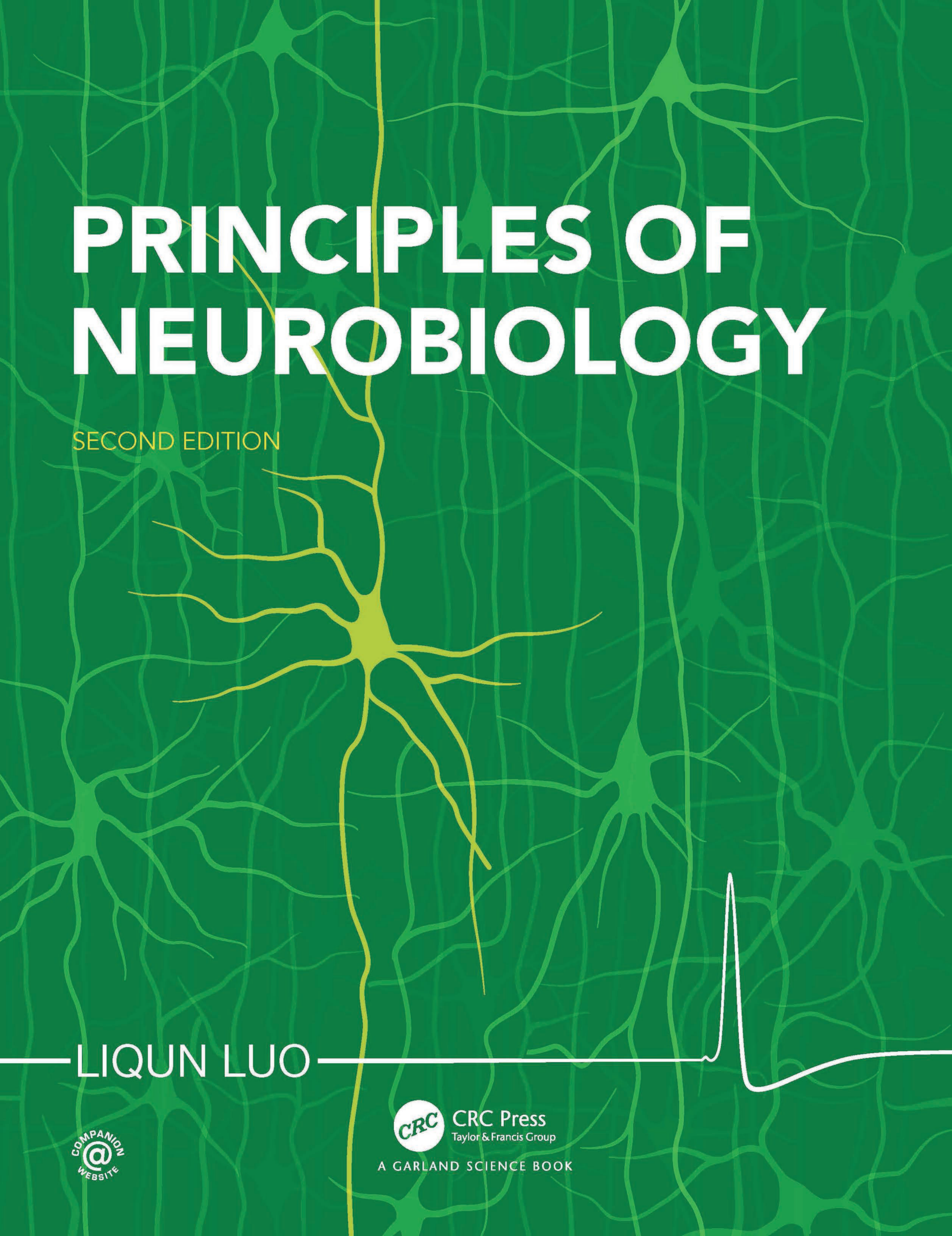

PRINCIPLES OF NEUROBIOLOGY

SECOND EDITION

LIQUN LUO

CRC Press
Taylor & Francis Group
A GARLAND SCIENCE BOOK

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

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-Specific Convention**		**Unified Convention 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.

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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.

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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

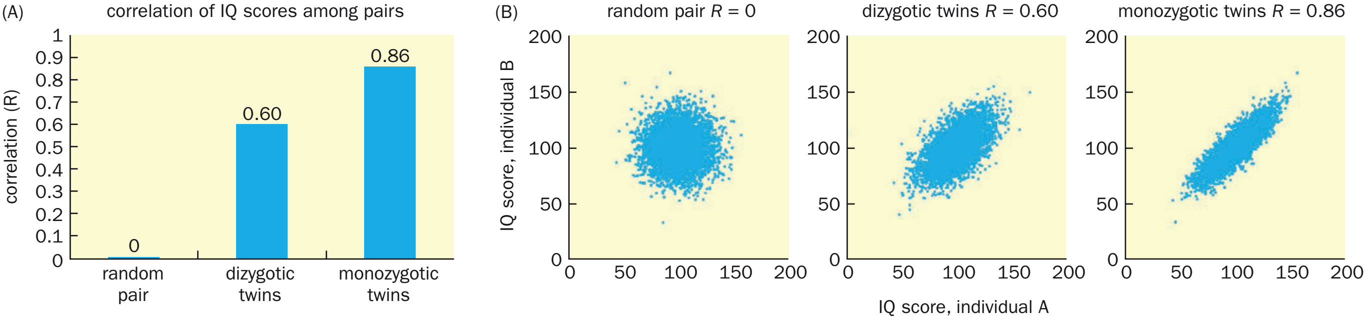

Figure 1-2 Twin studies for determining genetic and environmental contributions to intelligence quotient (IQ). (A) Correlation, or *R* value, of IQ scores for 4672 pairs of monozygotic twins and 5546 pairs of dizygotic twins. The correlation between the IQ scores of randomly selected pairs of individuals 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.

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**).

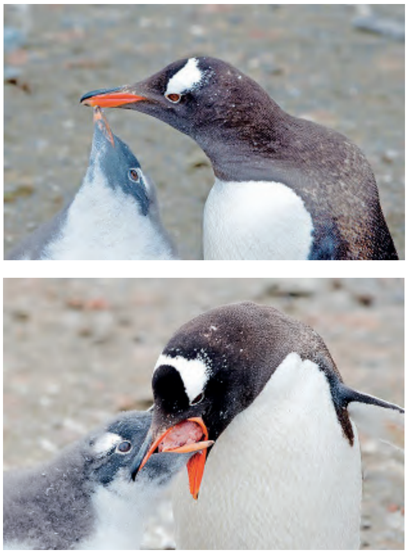

Figure 1-3 Penguin feeding. The instinctive behaviors of an adult penguin and its offspring photographed in Antarctica, 2009. Top, the young penguin asks for food by bumping its beak against its parent's beak. Bottom, the parent releases the food into the young penguin's mouth. (Courtesy of Lubert Stryer.)

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

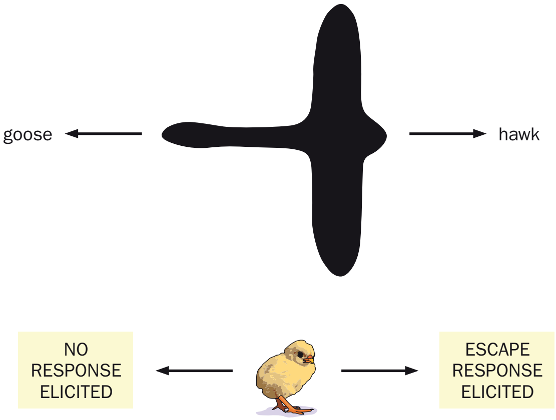

Figure 1-4 Innate escape response of a chick to a hawk. A young chick exhibits instinctive escape behavior in response to an object moving overhead that resembles a short-necked, hawk-like bird; moving the pictured object from left to right triggers this instinctive behavior. Moving the object from right 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

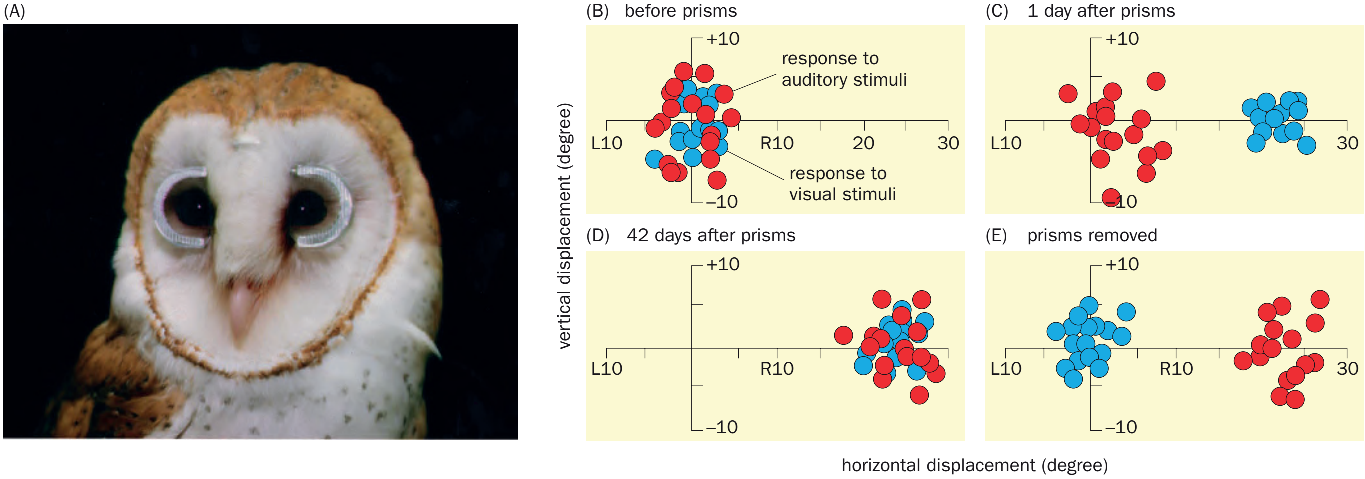

Figure 1-6 Juvenile barn owls adjust their auditory map to match a displaced visual map after wearing prisms. (A) A barn owl fitted with prisms that shift its visual map. **(B)** Before the prisms are attached, the owl's visual map (blue dots) and auditory map (red dots) are matched near 0°. Each dot 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.

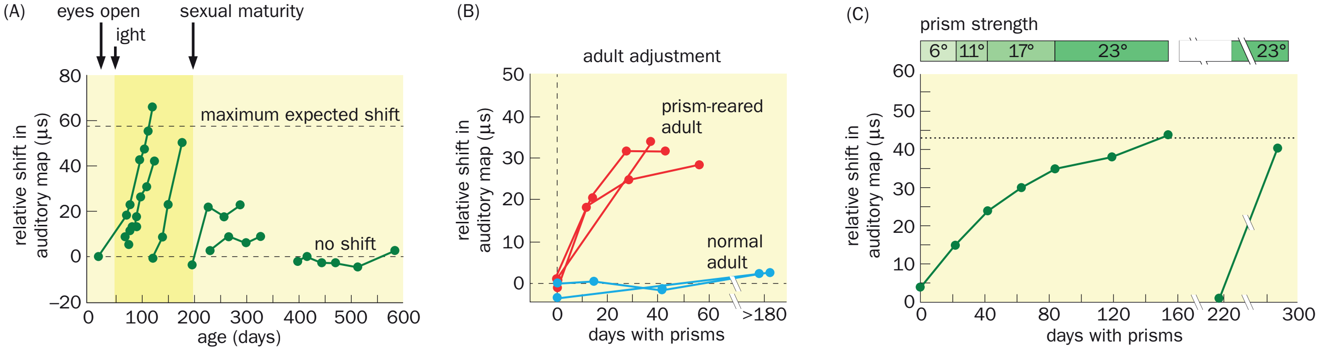

Figure 1-7 Ways to improve the ability of adult barn owls to adjust their auditory maps. (A) Owls' ability to adjust their auditory maps to match displaced visual maps declines with age. The *y* axis quantifies this ability to shift the auditory map, measured by the difference in time (μs, or microseconds) 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.)

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