

PRINCIPLES OF NEUROBIOLOGY

LIQUN LUO

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*To my parents, Chongxin Zhong and Kailian Luo,
who have granted me both nature and nurture.*

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PREFACE

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
<i>Caenorhabditis</i>	unc-6	UNC-6	Unc6	Unc6
<i>Drosophila</i>	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. The homework platform is available to everyone, though instructors will need to set up student access in order to use the dashboard to track student progress on assignments. The instructor's resources on the Garland Science website are password-protected and available only to adopting instructors. The student resources on the Garland Science website are available to everyone. We hope these resources will enhance student learning and make it easier for instructors to prepare dynamic lectures and activities for the classroom.

Online Homework Platform with Instructor Dashboard

Instructors can obtain access to the online homework platform from their sales representative or by emailing science@garland.com. Students who wish to use the platform must purchase access and, if required for class, obtain a course link from their instructor.

The online homework platform is designed to improve and track student performance. It allows instructors to select homework assignments on specific topics and review the performance of the entire class, as well as individual students, via

the instructor dashboard. The user-friendly system provides a convenient way to gauge student progress, and tailor classroom discussion, activities, and lectures to areas that require specific remediation. The features and assignments include:

- *Instructor Dashboard* displays data on student performance: such as responses to individual questions and length of time required to complete assignments.
- *Tutorials* explain essential or difficult concepts and are integrated with a variety of questions that assess student engagement and mastery of the material.
- *Media Assessments* present movies or explain complex figures from the book and contain a set of questions that assess student understanding of the concepts.
- *Quizzes* test basic reading comprehension and the retention of important terminology and facts. The quizzes are composed of multiple-choice and true-false questions.

The tutorials were created by Andrea Nicholas (University of California, Irvine) and the quizzes were written by Casey Guenthner (Neurosciences Program PhD student in the Luo Lab at Stanford University).

Instructor Resources

Instructor Resources are available on the Garland Science Instructor's Resource Site, located at www.garlandscience.com/instructors. The website provides access not only to the teaching resources for this book but also to all other Garland Science textbooks. Adopting instructors can obtain access to the site from their sales representative or by emailing science@garland.com.

Art of Principles of Neurobiology

The images from the book are available in two convenient formats: PowerPoint® and JPEG. They have been optimized for display on a computer. Figures are searchable by figure number, by figure name, or by keywords used in the figure legend from the book.

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

The animations and videos that are available to students are also available on the Instructor's Website in two formats. The WMV-formatted movies are created for instructors who wish to use the movies in PowerPoint presentations on Windows® computers; the QuickTime-formatted movies are for use in PowerPoint for Apple computers or Keynote® presentations. The movies can easily be downloaded using the 'download' button on the movie preview page. The movies are related to specific chapters and callouts to the movies are highlighted in color throughout the textbook.

Question Bank

Written by Elizabeth Marin (Bucknell University), 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.

Diploma® Test Generator Software

The questions from the Question Bank have been loaded into the Diploma Test Generator software. The software is easy to use and can scramble questions to create multiple tests. Questions are organized by chapter and type and can be additionally categorized by the instructor according to difficulty or subject. Existing questions can be edited and new ones added. The Test Generator is compatible with several course management systems, including Blackboard®.

Student Resources

The resources for students are available on the *Principles of Neurobiology* Student Website, located at www.garlandscience.com/neurobio-students

Journal Club

The Journal Club recommends journal articles that complement topics in the textbook to improve students' critical analysis of research and to promote a better understanding of the research process. Each Journal Club document provides background information on the chosen paper as well as questions and discussion points to stimulate in-class discussion. Answers will be provided to instructors only. The Journal Club was developed by Casey Guenthner (Neurosciences Program PhD student in the Luo Lab at Stanford University).

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 and can be searched or browsed.

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The author and publisher of *Principles of Neurobiology* specially thank Casey Guenthner (Stanford University) for creating the *Journal Club* and *Quizzes*, Melissa Coleman (Claremont McKenna, Pitzer and Scripps Colleges) and Lisa Marin (Bucknell College) for creating the *Question Bank*, and Andrea Nicholas (University of California, Irvine) for creating the *Tutorials*.

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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 is behavior controlled by the brain? How is the brain wired up during development? How do we sense the environment? What is changed in the brain when we learn something new? How much of our brain function and behavior is shaped by our genes, and how much reflects the environment in which we grew up? What about the contributions of genes and environment to the brain function and behavior of animals: monkeys, mice, frogs, or fruit flies? 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 mankind for thousands of years. Our ability to investigate and answer these questions experimentally is relatively recent: for example, the concept of the gene is only a century old. 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, the study of how the nervous system enables our sensation, action, thought, and memory. It is my hope that many readers of this book will be at the forefront of groundbreaking future discoveries.

NATURE AND NURTURE IN BRAIN FUNCTION AND BEHAVIOR

As an entrée to our journey, let's discuss one of the questions raised above 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 the 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 term nature versus nurture in the nineteenth century. He also introduced a powerful method to study the problem: the statistical analysis of human twins. Identical twins (Figure 1-1), also called **monozygotic twins**, share 100% of their genes because 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

Figure 1–1 Identical (monozygotic) twins. Identical twins develop from a single fertilized egg and therefore share 100% of their genes. Most identical twins also share a similar childhood environment. (Courtesy of Christopher J. Potter.)



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.) The correlation becomes 0.86 for identical twins (**Figure 1–2**), a striking similarity. However, identical twins also usually grow up in the same environment, so this correlation alone does not help us distinguish between the contributions of genes and the environment.

Fortunately, the human population provides a second group that allows researchers to tease apart the influence of genetic and environmental factors. Non-identical (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 a nearly identical prenatal and postnatal environment. Thus, the differences between traits exhibited by monozygotic and dizygotic twins should result from the differences in 50% of their genes. In our specific 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 calculated as the difference between the correlation of monozygotic and dizygotic twins multiplied by two (because the genetic difference is 50% between monozygotic and dizygotic twins). Thus, we have the heritability of IQ = $(0.86 - 0.60) \times 2 = 0.52$. Roughly speaking, then, about half of the IQ score variation among the human population is contributed by genetic differences, or nature. Traditionally, the non-nature component has been presumed to come from environmental factors, or nurture. However, 'environmental factors' as calculated in twin studies include all factors that are not inherited from parents' DNA. These include postnatal environment, which is what we typically think of as nurture, but also prenatal environment, stochasticity

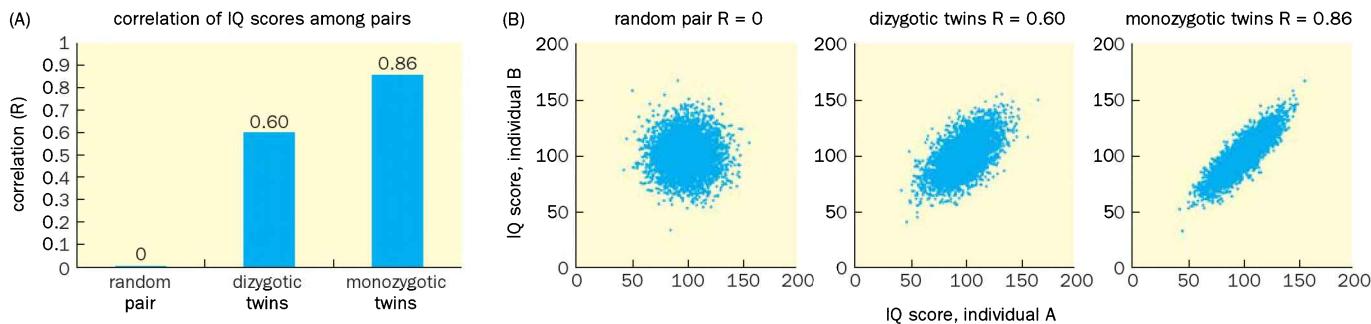


Figure 1–2 Twin studies for determining genetic and environmental contributions to intelligence quotient (IQ). (A) Correlation, or R value, of IQ scores for 4672 pairs of monozygotic twins and 5546 pairs of dizygotic twins. The correlation between the IQ scores of any two randomly selected individuals is zero. The difference in correlation between 100% genetically identical monozygotic twins and 50% genetically identical 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 individual pair. The simulations are based on a normal distribution of IQ scores (mean = 100, standard deviation = 15). (A, data from Bouchard TJ & McGue M [1981] *Science* 212:1055–1059.)

in developmental processes, somatic mutations (alterations of DNA after fertilization), and gene expression changes due to **epigenetic modifications** (that is, changes made to DNA and chromatin that do not modify the DNA sequence but can alter gene expression; epigenetic modifications typically include DNA methylation and various forms of post-translational modification of histones, the protein component of the chromatin). As we will learn later in the book, all these factors contribute to the wiring of the nervous system that ultimately determines brain 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 to 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 in many aspects of brain function and dysfunction in a given environment. The completion of the Human Genome Project and the development of tools that permit detailed examination of the genome sequence data, combined with the long history of medical and psychological studies of human subjects, has resulted in our own species becoming the subject of a growing body of neurobiological research. However, mechanistic understanding of how genes and the environment influence brain development, function, and behavior requires experimental manipulations that often can only be carried out in animal models. The use of vertebrate and invertebrate model species (see Sections 13.1–13.4) in research has yielded most of what we have learned about brain and behavior to date. Many principles of neurobiology obtained from experiments on specific animal models have turned out to be universally applicable to all organisms, including human beings.



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 to 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, directed by its food-seeking instinct, a baby penguin bumps its beak against that of its parent to remind the parent to feed it; in return, the parent instinctively releases the food it has foraged from the sea to feed the baby (**Figure 1–3**).

Instinctive behavior can be elicited by very specific sensory stimuli. For instance, experiments have been conducted to test the response of young chicks to an object that resembles a bird in flight, with the wings placed close to one end of the head-tail axis. When moved in one direction, the object looks like a short-necked, long-tailed hawk; when the direction of movement is reversed, the object appears gooselike, with a long neck and short tail. Upon 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

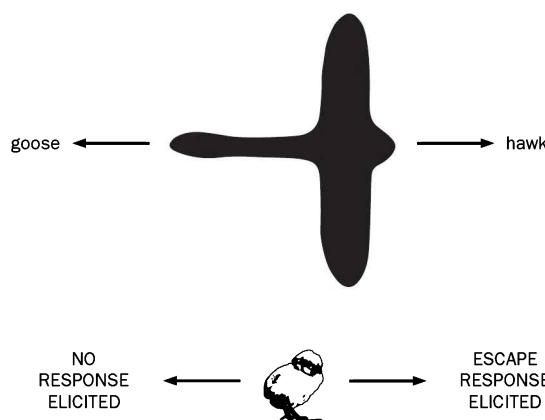


Figure 1–4 Innate escape response of chick to a hawk. A young chick exhibits instinctive escape behavior in response to an object moving overhead that resembles a short-necked, hawk-like bird; this instinctive behavior is triggered by moving the pictured object from left to right. Moving the object from right to left so that it resembles a long-necked goose does not elicit the chick's escape behavior. (Based on 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 image was constructed by superimposing a series of photographs taken with an infrared camera. (Courtesy of Masakazu Konishi.)

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 further sensory feedback. In **neuroethology**, a branch of science that emphasizes the study of animal behavior in the natural environment, such instinctive behavior is referred to as following a **fixed action pattern**. The essential features of the stimulus that activate the fixed action pattern are referred to as **releasers**.

How can genes and developmental programs specify such specific instinctive behaviors? In Chapter 9, we will use sexual behavior as an example to explore this question. For instance, we will learn about how a single gene in the fruit fly named *fruitless* can have a profound control of many aspects of the mating behavior.

1.3 An example of nurture: Barn owls adjust their auditory map to match an altered visual map

Animals also exhibit a remarkable capacity for learning in order to adapt to a changing world. We use the ability of barn owls adjusting their auditory map 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 locate accurately the source of sounds made by the prey, based on the small difference in the time it takes for a sound to reach their left and right ears. Using these time differences, the owl's brain creates a map of space, such that the activation of individual nerve cells at specific positions in this brain map informs the owl of the physical position of the prey.

Experiments in which prisms were attached over a barn owl's eyes (Figure 1–6A) revealed how the owl responds when its auditory and visual maps provide conflicting information. Normally, the auditory map matches the owl's visual map, so that perceptions of sight and sound direct the owl to the same location (Figure 1–6B). The prisms shift the owl's visual map by 23° to the right. On the first day after the prisms were placed onto a juvenile owl, a mismatch occurred between the owl's visual and auditory maps (Figure 1–6C): sight and sound

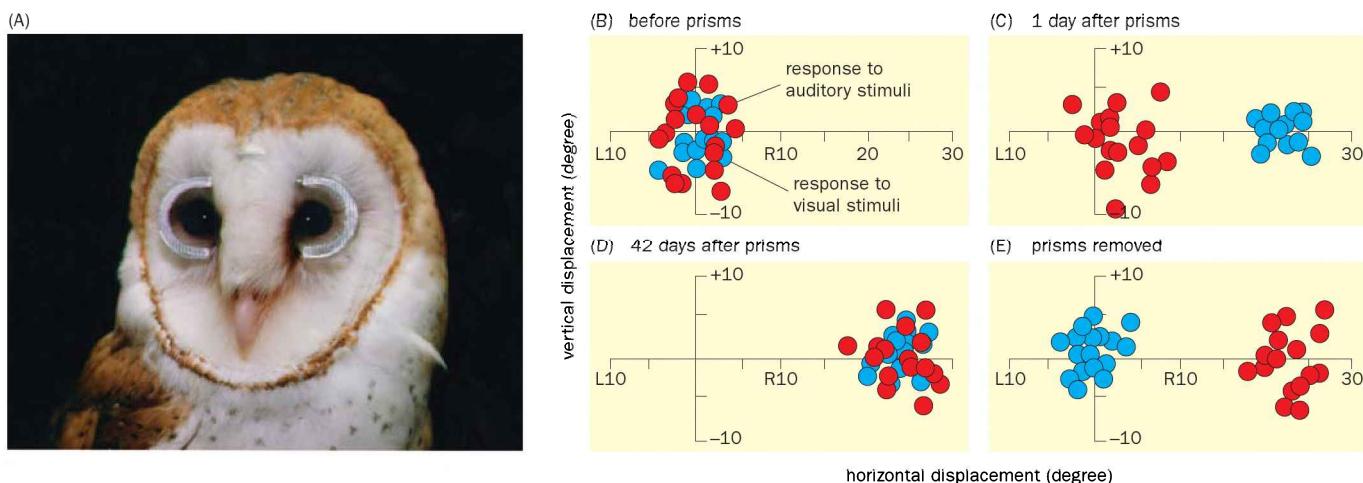


Figure 1–6 Juvenile barn owls adjust their auditory map to match a displaced visual map after wearing prisms. (A) A barn owl fitted with prisms that shift its visual map. (B) Before the prisms are attached, the owl's visual map (blue dots) and auditory map (red dots) are matched near 0°. Each dot represents an experimental measurement of owl's final head orientation in response to an auditory or a 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, adapted from Knudsen EI [2002] *Nature* 417:322–328. With permission from Macmillan Publishers Ltd.)

informed the owl of different locations for the prey, resulting in positional confusion. However, a juvenile owl could cope with this situation, perfectly adjusting its auditory map to match its altered visual map by 42 days after starting to wear the prisms (Figure 1-6D). When the prisms were removed, the mismatch happened again (Figure 1-6E), but the owl shifted the auditory map back to its native state shortly afterwards.

The story of the barn owl is an example of how the nervous system learns to cope with the changing world, a phenomenon called **neural plasticity**, that is, changes of the nervous system in response to experience and learning. But the story does not end there. 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 adult owls have lost the ability to do so by the time they reach sexual maturity (Figure 1-7A). Some human learning capabilities—such as ability to learn a foreign language—likewise decline with age. Thus, experiments on improving plasticity of adult owls may reveal strategies for improving the learning ability of adult humans as well.

Several ways have been found for adult owls to overcome their limited plasticity in shifting their auditory map. If an owl has the experience of adjusting to a 23°-prism shift as a juvenile, it can readjust much more readily 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 map if the visual field displacement is applied in small increments. Thus, by taking ‘baby steps,’ adult owls can eventually reach nearly the same magnitude of shift as young owls. Once they have learned to shift in gradual increments, the 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 that underlie 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 Chapter 10, we will return to this topic when we study memory and learning. Before addressing these concepts, however, we need to learn more basics about the brain and its building blocks. The rest of this chapter will give an overview of the nervous system and will explore how key historical discoveries helped build the conceptual framework of modern neuroscience.

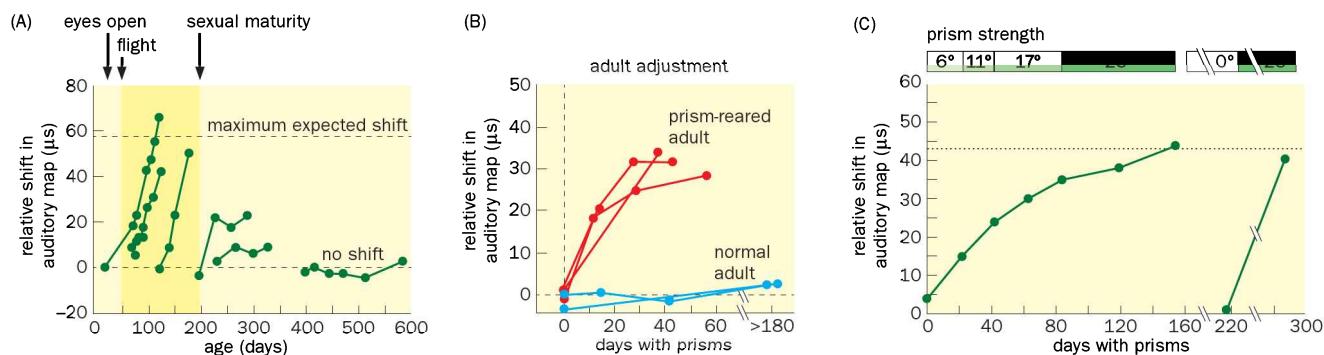


Figure 1-7 Ways to improve the ability of adult barn owls to adjust their auditory map. (A) The ability of owls to adjust their auditory map to match a displaced visual map declines with age. The y axis quantifies the ability to shift the auditory map, measured by the difference in time (μs , or microseconds) it takes for sounds to reach the left and right ears, used by the owl for object location. Each trace represents a single owl, with each dot representing the average of auditory map shift measured at a specific time after the prisms were applied. The shaded zone indicates the sensitive period, during which owls can easily adjust their auditory map in response to visual map displacement. Owls older than 200 days have only limited ability to shift their auditory map. (B) Three owls that had successful map adjustment to prism experience when

young can also shift their auditory map as adults (red traces). Two owls with no juvenile experience cannot shift their map as adults (blue traces). (C) Adult owls can also be trained to shift their auditory map by giving the prism shift in incremental steps, as shown on the left side of the graph. This incremental training enables adult owls to accommodate a sudden shift to the maximum visual displacement of 23° after a period without prism, as shown on the right side of graph. The dotted line at $y = 43 \mu\text{s}$ represents the median shift in juvenile owls in response to a single 23°-prism step. (A & B, adapted from Knudsen EI [2002] *Nature* 417:322–328. With permission from Macmillan Publishers Ltd; C, Linkenhoker BA & Knudsen EI [2002] *Nature* 419:293–296. With permission from Macmillan Publishers Ltd.)

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 1-8A, B). Both structures are bilaterally symmetrical; the two sides of the brain are referred as two **hemispheres**. The mammalian brain is composed of morphologically and

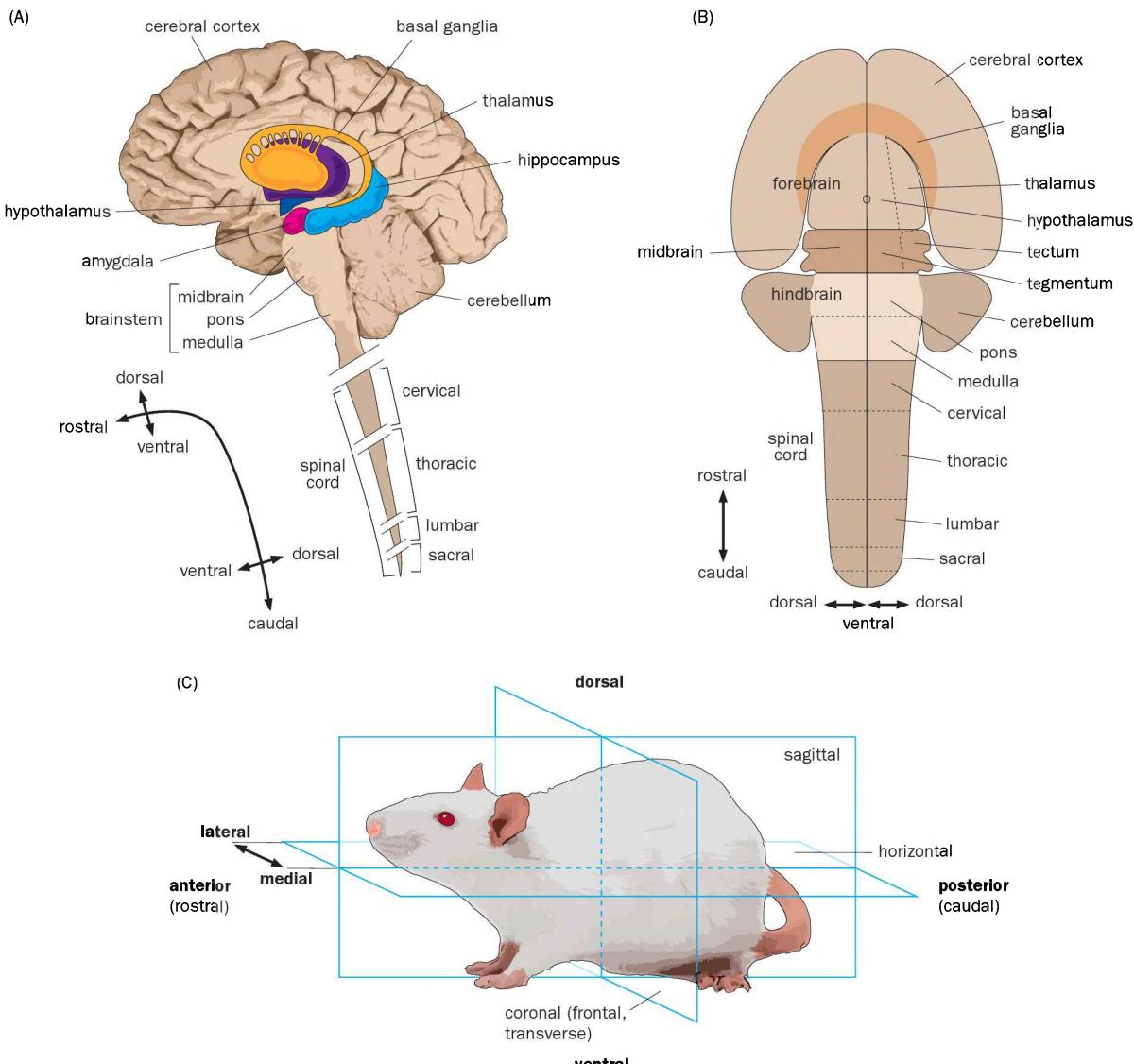


Figure 1-8 The organization of the mammalian central nervous system (CNS). (A) A sagittal (side) view of the human CNS. The basal ganglia (orange), thalamus (purple), hypothalamus (dark blue), hippocampus (light blue), and amygdala (red) from the left hemisphere are superimposed onto a mid-sagittal section of the rest 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. The spinal cord segments are divided into four groups: cervical, thoracic, lumbar, and sacral. 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 as cutting the CNS along the mid-sagittal 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, and the right side indicates major subdivisions. For example, the hypothalamus is ventral to the thalamus, and the midbrain is divided into tectum and tegmentum from dorsal to ventral. (C) Schematic illustration of the three principal section planes defined by the body axes. Coronal 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 that include 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. 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 comprises **nerves** (that is, discrete bundles of axons) that connect the brainstem and spinal cord of the CNS with the body and internal organs, as well as isolated **ganglia** (clusters 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 **coronal sections**, also called frontal, transverse, or cross sections, section planes are perpendicular to the **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). In animals with a curved CNS organization, the definition of rostral-caudal axis usually follows the **neuraxis** (axis of the CNS; bottom left of Figure 1-8A) rather than the body axis. The neural axis 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 of 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** often extends far beyond the cell body (**soma**). In contrast, the thick, bushy processes called **dendrites** are usually close to the soma (Figure 1-9A). At the ends of the axons are **presynaptic terminals**, specialized structures that participate in the transfer of information between neurons; the dendrites of many vertebrate neurons are decorated with small protrusions called **dendritic spines**, which likewise function in cell-to-cell information transfer. In the course of this book, we will encounter many neuronal types with distinct morphologies. Most of them have well-differentiated axons and dendrites, which serve distinct functions as will be discussed in Section 1.7.

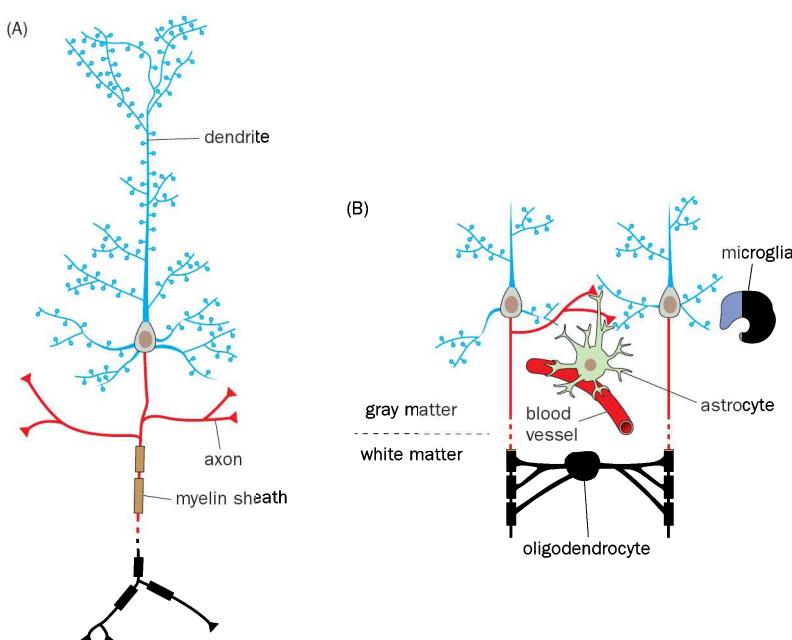


Figure 1–9 Neurons and glia.

(A) Schematic drawing of a typical neuron in the mammalian central nervous system (CNS). Dendrites are in blue, and the axon is in red. The dashed break in the axon indicates that it can travel a long distance from the cell body. The brown structures surrounding the axon are myelin sheath made from glia. The triangles at the ends of the axon branches represent presynaptic terminals, and the protrusions along the dendritic tree are dendritic spines, both of which will be discussed in subsequent sections.

(B) Schematic drawing of glia in the CNS. Oligodendrocytes wrap axons of the CNS neurons. (Schwann cells, not shown here, have a similar function in the peripheral nervous system.) Astrocytes have elaborate processes, whose end-feet wrap around the blood vessels, as well as connections between different neurons. Microglia are immune cells that engulf damaged cells and debris upon activation by injury and during developmental remodeling. (B, see Allen NJ & Barres BA [2009] *Nature* 457:675–677.)

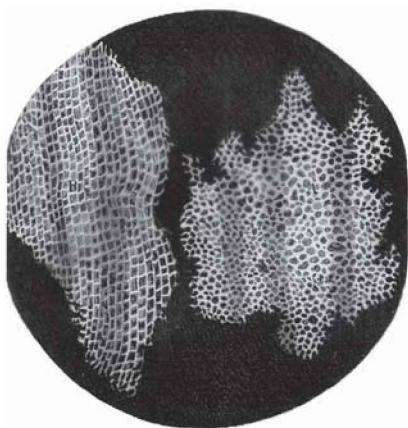


Figure 1–10 The first image of cells.

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 'cells' to describe them. (From Hooke R [1665] Micrographia. J. Martyn and J. Allestry.)

There are four major types of glia in the vertebrate nervous system: **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 increase the speed at which information propagates along axons. Oligodendrocytes and myelinated axons constitute the **white matter** in the CNS (because myelin is rich in lipids and appears white). Astrocytes play many roles in the 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, which engulf damaged cells and debris, and help reorganize neuronal connections. Invertebrate nervous systems have a similar division of labor for different glial types.

1.5 Individual neurons were first visualized by Golgi staining 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 that he observed in thin slices of cork (Figure 1–10) 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 basic units. The cell theory was well 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 the nervous tissues, many neurobiologists 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 the **reticular theory** regarded that the reticulum as a whole, rather than its individual cells, constituted the working unit of the nervous system.

Among the neuroscientists 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 destined for the cell surface, for other intracellular membranous organelles, or for secretion outside the cell. Golgi's greatest contribution, however, was the invention of the **Golgi staining** method. 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) form stochastically in a small fraction of the nerve cells so that these cells can be visualized against 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 staining, for the first time, enabled visualization of the entire morphology of individual neurons. However, despite inventing this key method for neuronal visualization, Golgi remained a believer in the reticular theory (see Box 1–1).

It took another great neuroscientist, Santiago Ramón y Cajal, to refute effectively 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 reticulum. Instead, neurons form intimate contact with each other, with communication between distinct neurons occurring at these contact points (see Box 1–1). The term **synapse** was later coined by Charles Sherrington to describe these sites at which signals flow from one neuron to

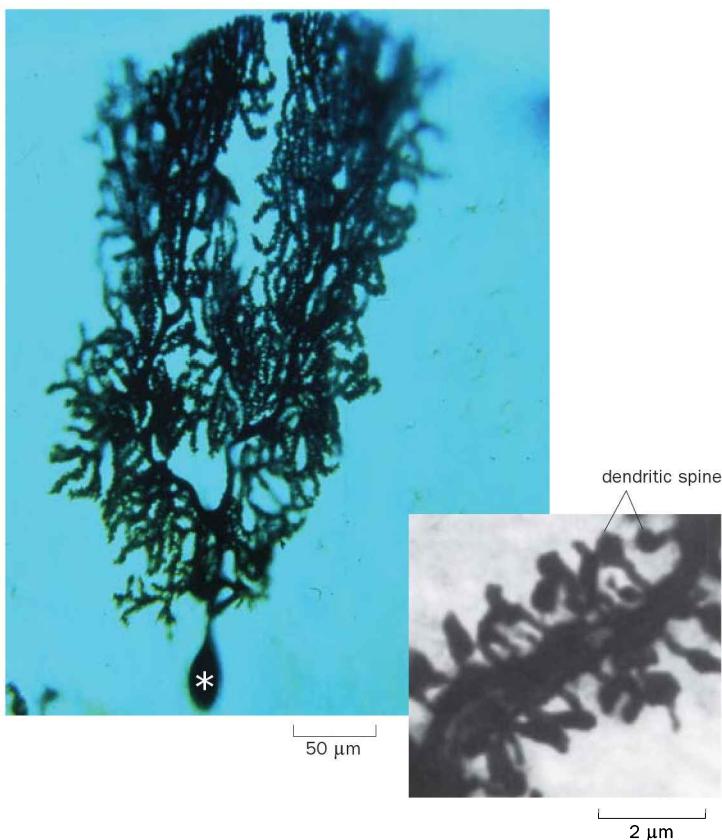


Figure 1-11 Golgi staining. An individual Purkinje cell in the mouse cerebellum is stained black by the formation of silver chromate precipitate, allowing visualization of its complex dendritic tree. The axon, which is not included in this image, projects downward from the cell body indicated by an asterisk.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

another. After systematically applying the Golgi staining method to study tissues in many parts of the nervous system, in many organisms ranging from insects to humans, and at many developmental stages, Ramón y Cajal concluded that individual neurons were 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 to neurobiologists. However, their debates on how nerve cells constitute the nervous system—by the reticular network or as individual neurons communicating with each other through synaptic contact—continued during their Nobel lectures (see **Figure 1-12A, B**). We now know that Ramón y Cajal's view was correct and Golgi's view was largely incorrect. For example, utilizing the brainbow labeling method (see Section 13.18 for more details), individual neurons, their dendritic tree, and even their axon terminals can be clearly distinguished by distinct colors (see **Figure 1-12C**). Interestingly, Ramón y Cajal used Golgi's staining method 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 the Golgi apparatus, a protein-processing organelle named after him.

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 staining method, neurobiologists could not resolve processes from individual nerve cells, and therefore believed that the nerve processes were fused together in a giant net. Golgi was trained in the scientific environment in which this reticular theory was the dominant interpretation of the nervous system organization. Golgi tried to fit his observations with existing theory. For example, even though Golgi was first to discover, using his staining method, that dendritic trees had free endings (**Figure 1-12A, top**), he thought that dendrites were

(Continued)

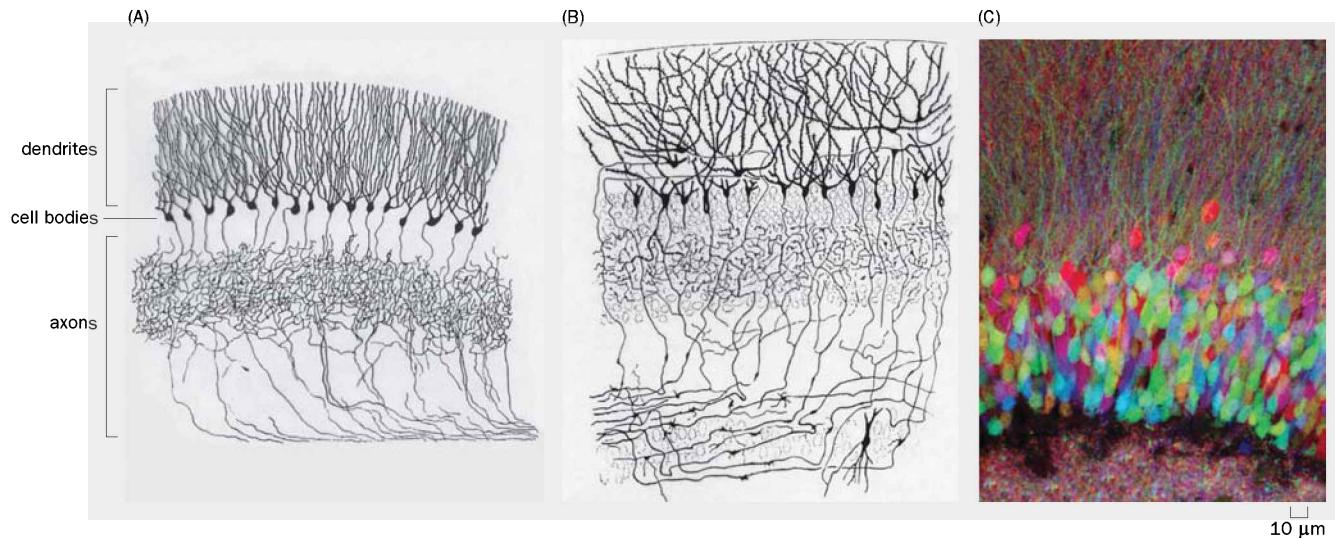
Box 1–1: The debate between Ramón y Cajal and Golgi: why do scientists make mistakes?


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 of their dendrites above and axon terminals below can be resolved by different colors. (A, adapted from Golgi C [1906] Nobel Lecture; B, adapted from Ramón y Cajal S [1911] Histology of the Nervous System of Man and Vertebrates. Oxford University Press; C, from Livet J, Weissman TA, Kang H et al. [2007] *Nature* 450:56–62. With permission from Macmillan Publishers Ltd.)

used to collect nutrients for nerve cells. 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 (see Box 1–1) have provided strong support for the neuron doctrine. For example, during embryonic development, neurons start out as having just the cell bodies. Axons then grow out from the cell bodies toward their final destinations. This was demonstrated by observing axon growth *in vitro* in experiments made possible by tissue culture techniques that were invented 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. We will learn more about the function of the growth cone in axon guidance in Chapter 5.

The final proof that neuronal processes do not fuse with each other came from observations made possible through the development of **electron microscopy**, a technique that allows the visualization of structures with nanometer (nm) resolution. (Conventional **light microscopy**, which scientists since Hooke have used to observe biological samples, cannot usually 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 the communication between cells is mediated by the release of chemicals called **neurotransmitters**) revealed that a 20–100 nm gap, the **synaptic cleft**, separates the neuron from its

target, which can be another neuron or a muscle cell (Figure 1–14A). The synaptic partners are not symmetrical: the presynaptic terminal of the neuron contains small **synaptic vesicles** filled with neurotransmitters, which, upon stimulation, fuse with the plasma membrane and release neurotransmitters into the synaptic cleft. The postsynaptic target cell develops a **postsynaptic specialization** (also called a **postsynaptic density**) that is enriched for the receptors on their plasma membrane surface to receive the neurotransmitters. Chemical synapses are the predominant type of synapses that allows 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 an alternative means: the **electrical synapse** mediated by the **gap junctions** between neurons (Figure 1–14B). Here, each partner neuron contributes protein subunits to form gap junction channels that directly link the cytoplasm of two adjacent neurons, allowing ions and small molecules to travel from one neuron to the next. These gap junctions probably 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 two 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 we introduced in Section 1.4, neurons have two kinds of processes: dendrites and axons. The shapes of dendritic trees and patterns of axonal projections are characteristic for particular types of neurons, and are often used to classify them. For example, the most frequently encountered type of neuron in the mammalian cerebral cortex and hippocampus, the **pyramidal neuron**, has a pyramid-shaped

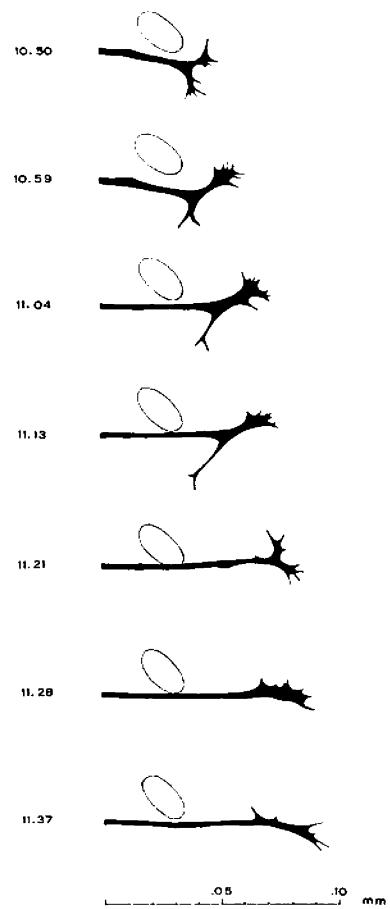


Figure 1–13 The first time-lapse depiction of a growing axon. Frog embryonic spinal cord tissue was cultured *in vitro*. Growth of an individual axon was sketched with an aid of a camera lucida at the time indicated on the left (hour:minute). The stationary blood vessel (oval) provided a landmark for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

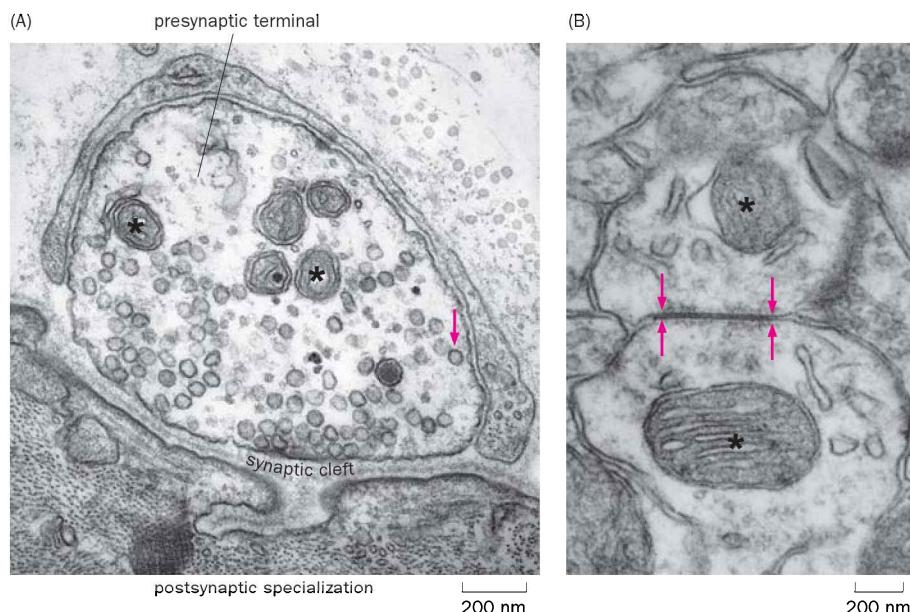


Figure 1–14 Chemical and electrical synapses. Asterisks indicate mitochondria in both micrographs. (A) Electron micrograph of a chemical synapse between the presynaptic terminal of a motor neuron and the postsynaptic specialization of its target muscle cell. A synaptic cleft separates the two cells. The arrow points at 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. (A, courtesy of Jack McMahan; B, courtesy of Josef Spacek and Kristen M. Harris, Synapse Web.)

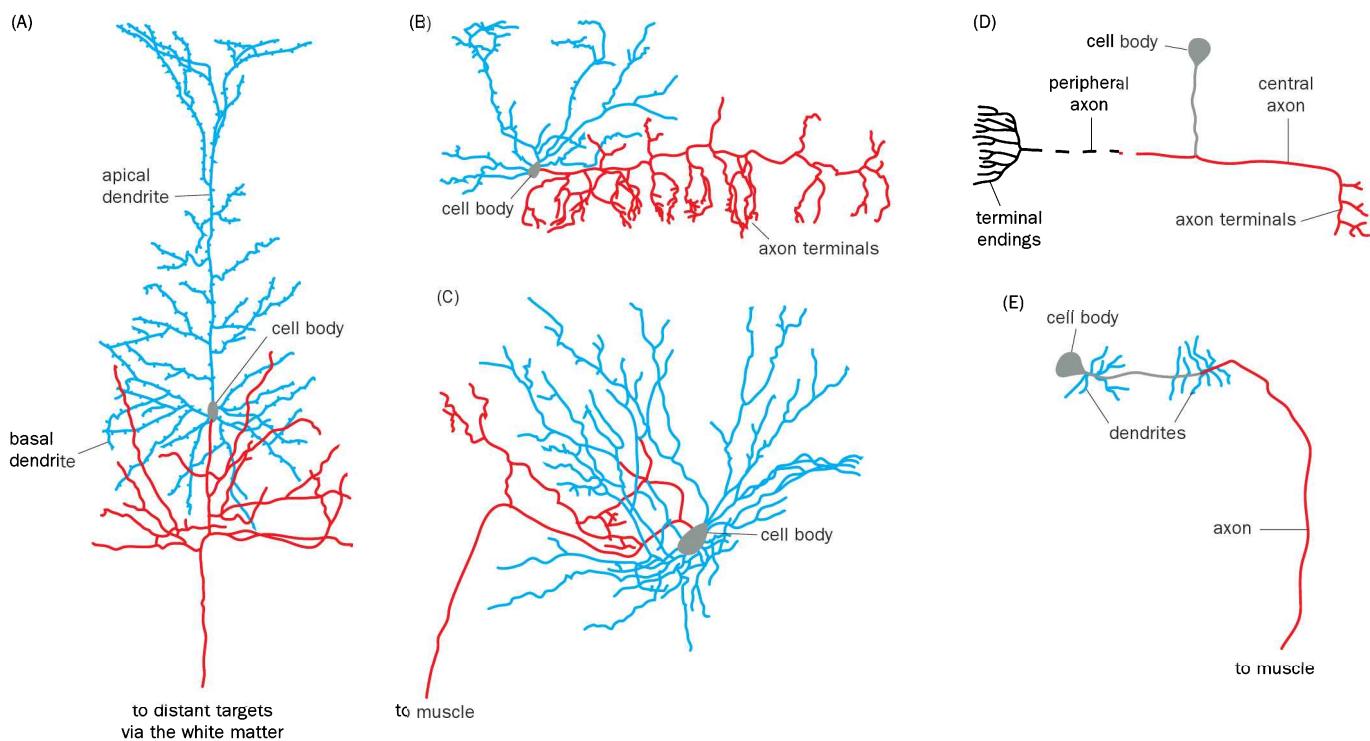


Figure 1–15 Some representative neurons. (A) A pyramidal cell from rabbit cerebral cortex. A typical pyramidal cell has an apical dendrite (blue) that gives off branches as it ascends, several basal dendrites (blue) that emerge from the cell body, and an axon (red) that branches locally and projects 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 the axon (red) extends outside the spinal cord to the muscle, while 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 with terminal endings in the skin (equivalent of dendrites that collect sensory information), and a central axon that project 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 comes out of the cell body, which gives rise to dendritic branches (blue) and the axon (red). (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.)

cell body with an apical dendrite and several basal dendrites that branch extensively (Figure 1–15A). A large portion of the dendritic tree is covered with dendritic spines (see Figure 1–11 inset), which contain postsynaptic specializations that are in close contact with presynaptic terminals of partner neurons. Another widely encountered type of neuron, **basket cells**, wrap their axon terminals around the cell bodies of pyramidal cells in the cerebral cortex or **Purkinje cells** (see Figure 1–11) in the cerebellum (Figure 1–15B). 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 the muscle. Located in a **dorsal root ganglion** just outside the spinal cord, a **sensory neuron** in the **somatosensory system** (which provides 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, hence they are called **multipolar** (or **bipolar** if there is only a single dendrite); somatosensory neurons are **pseudounipolar** as there is just one process leaving the cell body but it quickly gives rise to a peripheral and a central branch.

How does information flow within individual neurons? After systematically observing many types of neurons in different parts of the nervous system, Ramón y Cajal proposed a **theory of dynamic polarization**: the transmission of a neuronal signal takes place from dendrites and cell bodies to the axon. 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 complex vertebrate central nervous system. We will discuss the cell biological basis of neuronal polarization in Chapter 2.

How did observing the morphology of individual neurons lead to the discovery of this rule? Ramón y Cajal took advantage of the fact that, in sensory systems, information should 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, whereas 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. On the other hand, in the motor system, information should generally flow outward 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 the muscle provides the 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 central nervous system, is not as clear-cut as it is for vertebrate neurons. Most often, invertebrate neurons are **unipolar**, extending a single process that gives 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, paradoxically, 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 membrane potential changes 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 produce muscle twitches in frogs. It was known by the beginning of the twentieth century that electrical signals are propagated in neurons by transient changes of the **membrane potential**, the electrical potential difference across the neuronal membrane that reflects the distribution of positive and negative charges on each side of the membrane. As we will learn in more detail in Chapter 2, neurons in the resting state are more negatively charged inside the cells compared with the extracellular environment. 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 clearer when amplifiers for electrical signals were built in the 1920s that made it possible to record nerve impulses from single axon fibers in response to sensory stimulations. Edgar Adrian and co-workers systematically measured nerve impulses from somatosensory neurons (see 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; increasing the stimulus strength increased the frequency of such impulses, but not the inherent properties of each impulse (Figure 1–17).

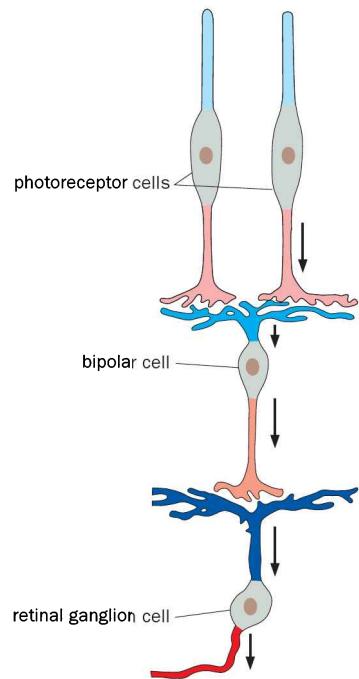
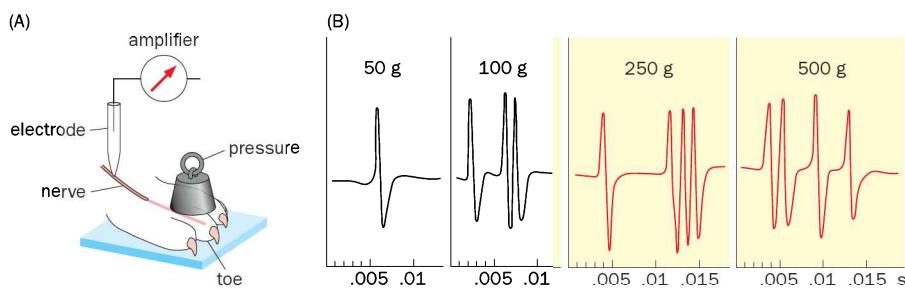


Figure 1–16 Neurons and information flow in the vertebrate retina. Visual information is collected by photoreceptor cells in the retina. It is communicated to the bipolar cell and then to the retinal ganglion cell, which projects a long-distance axon into the brain. Note that for both the bipolar cell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

Figure 1–17 Stimulus strengths are encoded by the frequency of uniformly sized nerve impulses. (A) Experimental setup for applying a specified amount of pressure to the toe of a cat, while recording impulses from an associated sensory nerve. (B) As the pressure applied to a cat's toe increases, the frequency of impulses measured at the sensory nerve increases, but the size and shape of each impulse remain mostly the same. We now call these nerve impulses action potentials. The x axis shows the timescale in units of seconds (s). (Adapted from Adrian ED & Zotterman Y [1926] *J Physiol* 61:465–483.)



These experiments led to two important concepts of 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 being delivered. 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 using action potentials to send signals across long distances within the axons of individual neurons, another important form of communication within neurons are **graded potentials** (also called **local potentials**), referring to membrane potentials that can change in continuous values as opposed to all-or-none. One type of graded potentials, termed **synaptic potentials**, is produced at the postsynaptic sites in response to neurotransmitter release by presynaptic partners. Graded potentials can also be induced at the peripheral endings of sensory neurons by sensory stimuli, such as the pressure on the toe in Adrian's experiment mentioned above; these are termed **receptor potentials**. Unlike action potentials, graded potentials are of different sizes depending on the strength of the input stimuli and the sensitivity of postsynaptic or sensory neurons to those stimuli. Some neurons, including most neurons in the vertebrate retina, do not fire action potentials at all. These **non-spiking neurons** use graded potentials to transmit information even in their axons.

Synaptic potentials are usually produced at the dendritic spines, along the dendrite tree, and at the soma of a neuron. A typical mammalian neuron contains thousands of postsynaptic sites on its dendrite tree, allowing it to collect input from many individual presynaptic partners (Figure 1–18). Inputs that are excitatory facilitate action potential production by the postsynaptic neuron, whereas inhibitory inputs dampen action potential production by the postsynaptic neuron. In most neurons, the eventual purpose of all these synaptic potentials is to determine whether, when, and how frequently the neuron will fire action potentials, so that information can propagate along its axon to its own postsynaptic target neurons. The site of action potential initiation is typically at the **initial segment of the axon**, adjacent to the soma. Thus, synaptic potentials generated in dendrites must travel to the cell body in order to have their voices heard.

The rule of action potential initiation at the axon initial segment has exceptions. For example, in the sensory neuron in Figure 1–15D, action potentials are initiated at the junction between terminal endings and the peripheral axon of the sensory neuron such that sensory information can be transmitted by the peripheral and central axon to the spinal cord across a long distance. In invertebrate neurons, which are mostly unipolar, action potential initiation likely occurs at the junction between the dendritic and axonal compartments.

How is information transmitted between neurons? At electrical synapses, membrane potential changes are directly transmitted from one neuron to the next by ion flow across the gap junctions. At chemical synapses, the arrival of action potentials (or graded potentials in non-spiking neurons) at the presynaptic terminals triggers the release of neurotransmitters. Neurotransmitters diffuse

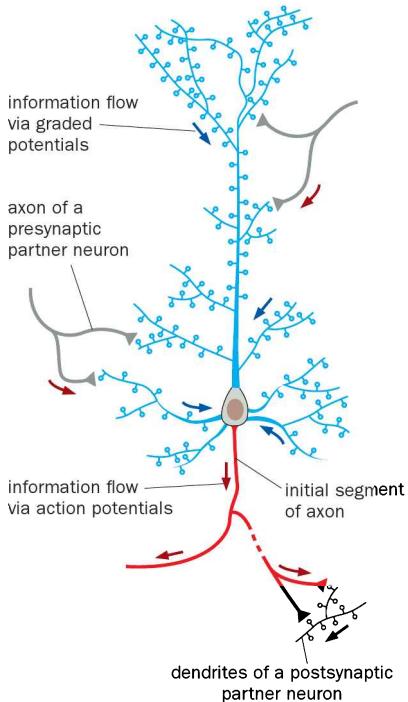


Figure 1–18 Fundamental steps of neuronal communication. A typical neuron in the mammalian CNS receives thousands of inputs distributed along the dendrite tree and dendrite spines (blue), where this neuron is postsynaptic to its presynaptic partners. Inputs are collected in the form of synaptic potentials, which travel toward the cell body (blue arrows) and are integrated at the initial segment of the axon (red) to produce action potentials. Action potentials propagate to the axon terminals (red arrows), and trigger neurotransmitter release that conveys information to many of its postsynaptic partner neurons.

across the synaptic cleft and bind to their receptors on the postsynaptic neurons to produce synaptic potentials (Figure 1–18). The process of neurotransmitter release from the presynaptic neuron and neurotransmitter reception by the postsynaptic neuron is collectively referred to as **synaptic transmission**. Thus, while intraneuronal communication is achieved by membrane potential changes in the form of graded potentials and action potentials, interneuronal communication at chemical synapses relies on neurotransmitter release and reception. We will study these fundamental steps of neuronal communication in greater detail in Chapters 2 and 3.

1.9 Neurons function in the context of specific neural circuits

Neurons perform their functions in the context of **neural circuits**, which are ensembles of interconnected neurons that act together to perform specific functions. The simplest circuits in vertebrates, those that mediate the spinal reflexes, can consist of as few as two interconnected neurons: a sensory neuron that receives sensory stimuli from the environment, and a motor neuron that controls muscle contraction. Many fundamental neurobiological principles have been derived from studying these simple circuits.

When a neurologist's hammer hits the knee of a patient during a neurological exam, the lower leg kicks forward involuntarily (Figure 1–19). The underlying circuit mechanism for this **knee-jerk reflex** has been identified. Sensory neurons embed their endings in specialized apparatus called **muscle spindles** in an extensor muscle (a muscle whose contraction will extend the knee joint). These sensory neurons detect the stretch of the muscle spindles caused by the physical impact of the hammer and convert the mechanical stimuli into electrical signals, namely receptor potentials at the sensory endings. Next, the peripheral and central axons of the sensory neurons propagate these electrical signals to the spinal cord as action potentials. There, the central axons of the sensory neurons make synaptic connections directly with the dendrites of motor neurons, which extend their own axons outward from the spinal cord and terminate in the same extensor muscle where the sensory neurons embed their endings. (The sensory axons are also called **afferents**, referring to axons projecting from peripheral tissues to the CNS, whereas the motor axons are called **efferents**, referring to axons that project from the CNS to peripheral targets.) Both the sensory and motor neurons in this circuit are **excitatory neurons**. When excitatory neurons are activated, that is, when they fire action potentials and release neurotransmitters, they make their postsynaptic target cells more likely to fire action potentials. Therefore, mechanical stimulation activates sensory neurons. Their excitation in turn activates their postsynaptic motor neurons, causing them to fire action potentials. Action potentials from the motor neurons cause neurotransmitter release at motor axon terminals in the muscle, causing the contraction of the extensor muscle that they innervate.

The knee-jerk reflex involves the coordination of more than one muscle. The flexor muscle, which is antagonistic to the extensor muscle, must *not* contract at the same time in order for the knee-jerk reflex to occur. (As we will learn in Chapter 8, contraction of extensor muscles increases the angle of a joint, whereas contraction of flexor muscles decreases the angle of a joint.) Therefore, in addition to causing the contraction of the extensor muscle, the sensory axons must also inhibit the contraction of the corresponding flexor muscle. This inhibition is mediated by **inhibitory interneurons** in the spinal cord, a second type of postsynaptic neuron targeted by the sensory axons. (Neurobiologists use the term **interneuron** in two different contexts. In a broad context, all neurons that are not sensory or motor neurons are interneurons. In more a specific context, interneurons refer to neurons that confine their axons within a specific region—as opposed to **projection neurons**, whose axons link two different regions of the nervous system. The spinal inhibitory interneurons fit both criteria.) Activation of sensory neurons excites these inhibitory interneurons, which in turn inhibit the motor neurons that innervate the flexor muscle. The inhibition makes it more difficult for the flexor motor neurons to fire action potentials, causing the flexor

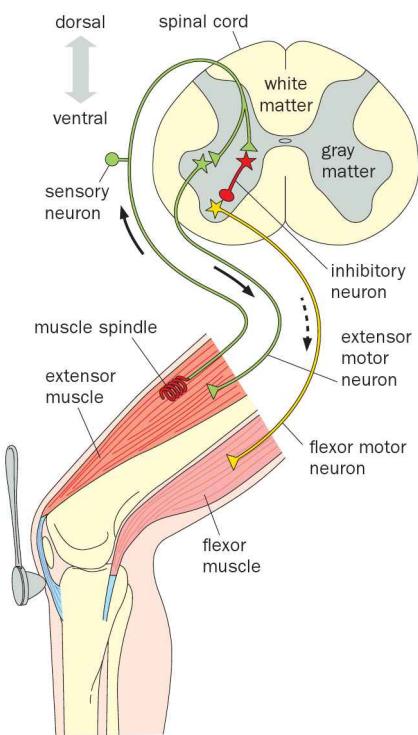


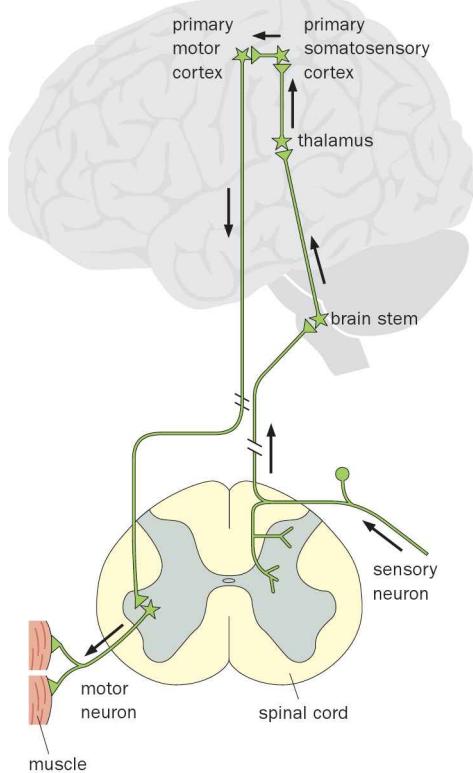
Figure 1–19 The neural circuit underlying the knee-jerk reflex. A simple neural circuit is responsible for the involuntary jerk that results when the front of the human knee is hit with a hammer. In this simplified scheme, a single neuron is used to represent a population of neurons that perform the same task. The sensory neuron extends its peripheral axon to the muscle spindle of the extensor muscle and its central axon to the spinal cord. In the spinal cord, the sensory neuron has two postsynaptic targets: the green motor neuron that innervates the extensor muscle, and the red inhibitory interneuron within the spinal cord, which synapses with the yellow motor neuron that innervates the flexor muscle. When the hammer hits the knee, mechanical force excites the sensory neuron, which results in excitation of the extensor motor neuron to cause contraction of the extensor muscle (following solid arrows) and inhibition of the flexor motor neuron to cause relaxation of the flexor muscle (dashed arrow). The spinal cord is drawn as a cross section. The gray matter at the center contains cell bodies, their dendrites, and the synaptic connections of spinal cord neurons; the white matter at the periphery consists of long-distance axonal projections. The sensory neuron cell body is located in a dorsal root ganglion adjacent to the spinal cord.

muscle to relax. Contraction of the extensor muscle is coordinated with relaxation of the flexor muscle to bring the lower leg forward. First analyzed in the studies of spinal reflexes by Charles Sherrington in the 1890s, the role of inhibition is crucial in coordinating neuronal function throughout the nervous system.

Thus, the knee-jerk reflex involves one of the simplest neural circuits, in which coordinated actions of excitation and inhibition are performed by the monosynaptic connections between sensory neurons and motor neurons and the disynaptic connections between sensory neurons and a different group of motor neurons via inhibitory neuron intermediates. Nervous system functions rely on establishing proper connections between neurons in numerous neural circuits like the knee-jerk reflex circuit; how the nervous system is precisely wired during development is a subject that we will focus on in Chapters 5 and 7.

Most neural circuits are orders of magnitude more complex than the spinal cord reflex circuit. **Box 1–2** discusses commonly used circuit motifs that we will encounter in this book. For example, a subject becomes aware that a hammer has hit her knee because sensory neurons also send branches of axons that ascend along the spinal cord. After passing through relay neurons in the brainstem and thalamus, sensory information eventually reaches the **primary somatosensory cortex**, the part of the cerebral cortex that first receives somatosensory input from the body (Figure 1–20). Cortical processing of such sensory input gives her the perception that the knee has been hit. Such information is also propagated to other cortical areas including the **primary motor cortex**. The primary motor cortex sends descending output directly and indirectly to the spinal cord motor neurons to control muscle contraction (Figure 1–20), in case we want to move our leg voluntarily (as compared to the knee-jerk reflex, which is involuntary). We will study these sensory and motor pathways in greater details in Chapters 6 and 8, but in general we know far less about the underlying mechanisms of the ascending, cortical, and descending circuits compared to the reflex circuit in the spinal cord. Deciphering the principles of information processing in complex neural circuits that mediate sensory perception and motor control is one of the most exciting and challenging goals of modern neuroscience.

Figure 1–20 Schematic of sensory and motor pathways between the spinal cord and the cerebral cortex. In addition to participating in the spinal cord reflex circuit, sensory neurons also send an ascending branch to connect with relay neurons in the brainstem and thalamus to deliver information to neurons in the primary somatosensory cortex. Through inter-cortical connections, information can be delivered to neurons in the primary motor cortex, which send descending output directly and indirectly to motor neurons for the voluntary control of muscles. Drawn here are the most direct routes for these ascending and descending pathways. The spinal cord is represented as a cross section. The brain in the background is from a sagittal view (not at the same scale as the spinal cord). Arrows indicate the direction of information flow.



Box 1–2: Commonly used neural circuit motifs

The simplest circuit consists of two synaptically connected neurons, such as the sensory neuron-extensor motor neuron connection in the knee-jerk reflex. In circuits that contain more than two neurons, the individual neurons can receive input from and send output to more than one partner. Further complexity arises when some neurons in a circuit are excitatory and others are inhibitory. The nervous system employs many circuit motifs, that is, different ways in which circuits can be configured so that the connection patterns of individual neurons combine to carry out specific functions. We introduce here some of the most commonly used circuit motifs (Figure 1–21).

Let's first consider circuits that contain only excitatory neurons. When several neurons synapse onto the same postsynaptic neuron, this constitutes the circuit motif of convergent excitation (Figure 1–21A). Conversely, divergent excitation (Figure 1–21B) refers to the motif where a single neuron synapses onto multiple postsynaptic targets via branched axons (these axon branches are also called **collaterals**). Convergent and divergent connections allow individual neurons to integrate input from multiple presynaptic neurons, and to send output to multiple postsynaptic targets. Serially connected excitatory neurons constitute a **feedforward excitation** motif (Figure 1–21C) to propagate information across multiple regions of the brain, such as the relay of somatosensory stimuli to the primary

somatosensory cortex (see Figure 1–20). If a postsynaptic neuron synapses onto its own presynaptic partner, this would produce a feedback excitation motif (Figure 1–21D). Neurons that transmit parallel streams of information can also excite each other, forming a motif of recurrent (lateral) excitation (Figure 1–21E).

When excitatory and inhibitory neurons interact in the same circuit, as is most often the case, many interesting circuit motifs can be constructed and used for different purposes. The names of these motifs that involve inhibitory neurons usually emphasize the nature of the inhibition. In **feedforward inhibition** (Figure 1–21F), an excitatory neuron synapses onto both an excitatory and an inhibitory postsynaptic neuron, and the inhibitory neuron further synapses onto the excitatory postsynaptic neuron. In **feedback inhibition** (Figure 1–21G), the postsynaptic excitatory neuron synapses onto an inhibitory neuron, which synapses back to the postsynaptic excitatory neuron. In both cases, inhibition can control the duration and the magnitude of the excitation of the postsynaptic excitatory neuron. In **recurrent (cross) inhibition** (Figure 1–21H), two parallel excitatory pathways cross-inhibit each other via inhibitory neuron intermediates; the inhibition of the flexor motor neuron in the knee-jerk reflex discussed in Section 1.9 is an example of recurrent inhibition. In **lateral inhibition** (Figure 1–21I), an inhibitory neuron receives excitatory input from one or several parallel streams of excitatory neurons, and sends inhibitory output to many postsynaptic targets of these excitatory neurons. Lateral inhibition is widely used in processing sensory information, as we will study in greater detail in Chapters 4 and 6. Finally, when an inhibitory neuron synapses onto another inhibitory neuron, the excitation of the first inhibitory neuron reduces the inhibitory output of the second inhibitory neuron, causing **disinhibition** of the target of the second inhibitory neuron (Figure 1–21J).

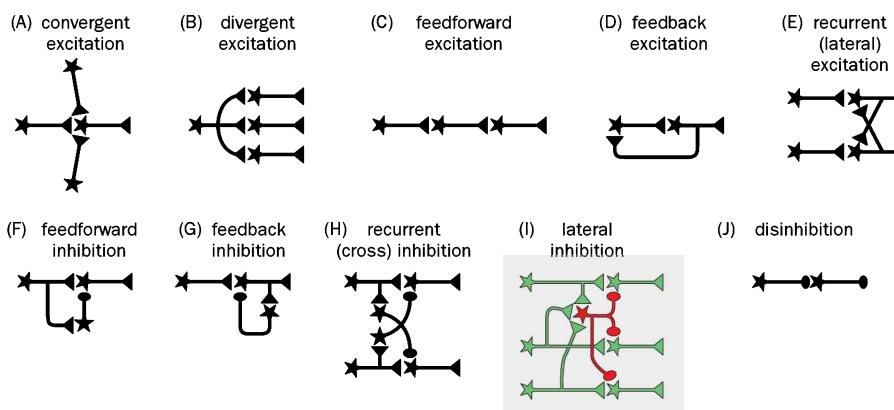
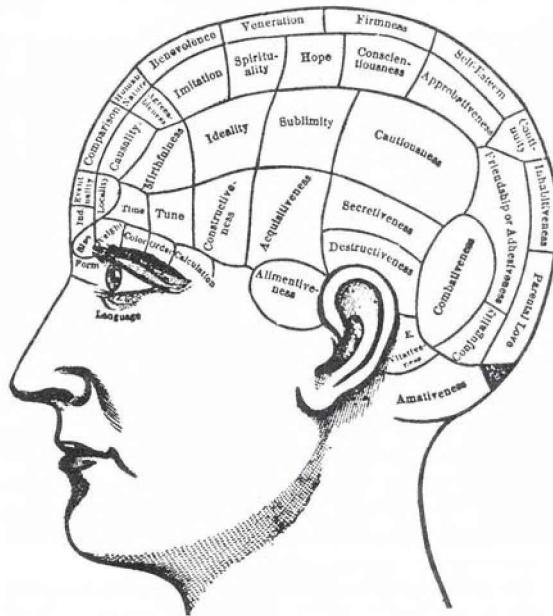


Figure 1–21 Commonly used circuit motifs. In all panels, the general information flow is from left to right. (A–E) Circuit motifs consisting of excitatory neurons. These include convergent excitation (A), in which multiple neurons synapse onto the same neuron; divergent excitation (B), in which a single neuron synapses onto multiple target neurons; feedforward excitation (C), in which neurons are connected in series; feedback excitation (D), in which the postsynaptic neuron synapses onto its presynaptic partner; and recurrent excitation (E), in which two parallel pathways cross excite each other. (F–J) Circuit motifs that include inhibitory neurons. In feedforward inhibition (F), the inhibitory neuron receives input from a presynaptic excitatory neuron and sends output to a postsynaptic excitatory neuron, whereas in feedback inhibition (G), the inhibitory neuron receives input from and sends output to the postsynaptic excitatory neuron. For recurrent inhibition (H) and lateral inhibition (I), only feedforward modes are depicted; in the feedback modes of these motifs (not shown), the inhibitory neuron(s) receive input(s) from postsynaptic rather than the presynaptic excitatory neurons in the parallel pathways. In the disinhibition motif (J), the target of the second inhibitory neuron (not shown) can be excitatory or inhibitory. When the first inhibitory neuron is excited, the target of the second inhibitory neuron becomes disinhibited, because excitation of the first inhibitory neuron causes the second inhibitory neuron to be less active.

Circuit motifs containing excitatory and inhibitory neurons are often used in combinations that give rise to many different ways of processing information in complex nervous systems. In Chapter 3, we will encounter another group of neurons, the **modulatory neurons**, which can act on both excitatory and inhibitory neurons to up- or down-regulate their excitability or synaptic transmission, adding further complexity and richness to the information processing functions of neural circuits.

Figure 1–22 Phrenologists' depiction of the brain's organization. According to phrenology, the brain is divided into individual areas specialized for defined mental functions. The size of each area is modified by use. For example, a cautious person would have an enlarged area corresponding to cautiousness.



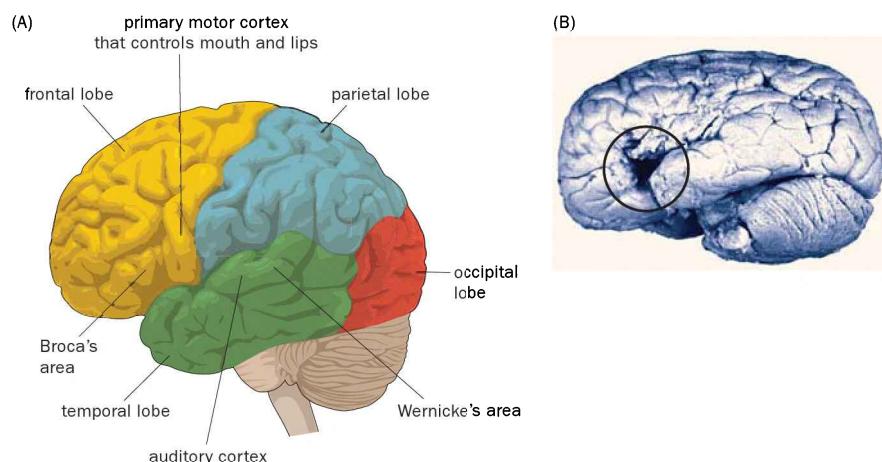
1.10 Specific brain regions perform specialized functions

That specialized functions of the nervous system are performed by specific parts of the brain is well established today. However, throughout prior centuries, philosophers have debated whether brain functions underlie the mind, let alone whether specific regions of the brain are responsible for specific mental activities. Even in the early twentieth century, a prevalent view was that any specific mental function is carried out by neurons across many areas of the cerebral cortex.

Franz Joseph Gall developed a discipline called **phrenology** in the early nineteenth century. Gall believed that all behavior emanates from the brain, with specific regions of the brain controlling specific functions. According to Gall, the centers for each mental function grow with use, creating bumps and ridges on the skull. Based on this proposal, Gall and his followers attempted to map human mental function to specific parts of the cortex, correlating the size and shape of the bumps and ridges on a person's skull with their talents and character traits (Figure 1–22). We now know that the specific conclusions of phrenology are largely false, but Gall's thinking about brain specialization was quite advanced for his time.

Brain lesions provided the first clues that specialized regions of the human cerebral cortex carry out specific functions. Each hemisphere of the cerebral cortex is divided into four lobes based on the major folds (called **fissures**) that separate the lobes: the **frontal lobe**, **parietal lobe**, **temporal lobe**, and **occipital lobe** (Figure 1–23A). In the 1860s, Paul Broca discovered lesions in a specific area

Figure 1–23 Language centers in the human brain were originally defined by lesions. (A) Major fissures divide each hemisphere of cerebral cortex into frontal, parietal, temporal, and occipital lobes. Broca's area is located in the left frontal lobe adjacent to the part of the primary motor cortex that controls movement of mouth and lips (see Figure 1–25). Wernicke's area is located in the left temporal lobe adjacent to the auditory cortex. (B) Photograph of the brain from one of Broca's patients, Leborgne, who could only speak a single syllable, "tan." The lesion site is circled. Observation of similar lesions in language-deficient patients led Broca to propose the area to be essential for language production. (B, from Rorden C & Karnath H [2004] *Nat Rev Neurosci* 5:813–819. With permission from Macmillan Publishers Ltd.)



of the human left frontal lobe (Figure 1–23B) in patients who could not speak. This area was subsequently named **Broca's area** (Figure 1–23A). Karl Wernicke subsequently found that lesions in a distinct area in the left temporal lobe, now named **Wernicke's area** (Figure 1–23A), were also associated with defects in language. Interestingly, lesions in Broca's area and Wernicke's area give distinct symptoms. Patients with lesions in Broca's area have great difficulty in producing language, whether in speech or in writing, but their understanding of language is largely intact. On the other hand, patients with lesions in Wernicke's area have great difficulty in understanding language, but they can speak fluently, although often unintelligibly and incoherently. These findings led to the proposal that Wernicke's area is responsible for language comprehension whereas Broca's area is responsible for language production. These distinct functions are consistent with the locations of Broca's and Wernicke's areas being close to the motor cortex and the **auditory cortex** (the part of the cortex that first receives auditory sensory input), respectively (Figure 1–23A).

In the twentieth century, two important techniques—brain stimulation and brain imaging—have confirmed and extended findings from lesion studies, revealing in greater detail specific brain regions that carry out distinct functions. Brain stimulation has been used as a standard procedure to map specific brain regions in order to guide brain surgeries, such as severing axonal pathways to treat intractable **epilepsy**. (Epilepsy is a medical condition characterized by recurrent seizures, which are strong surges of abnormal electrical activity that affects part or all of the brain; we will study epilepsy in more detail in Chapter 11.) Such surgeries are often performed without general anesthesia (as brains do not contain pain receptor) so that patients' responses to brain stimulation can be assessed. Stimulation of Broca's area, for instance, causes a transient arrest of speech in patients. These brain stimulation studies have identified additional areas that interfere with language production.

One of the most remarkable advances in the late twentieth century is the non-invasive functional brain imaging of healthy human subjects as they perform specific tasks. The most widely used technique is **functional magnetic resonance imaging (fMRI)**, which monitors signals originating from changes in blood flow that are closely related to local neuronal activity. By allowing researchers to observe whole-brain activity without bias while subjects perform intensive tasks, such as those involving language, fMRI has revolutionized our understanding of specific brain regions that are implicated in specific functions. Such studies have confirmed that Broca's and Wernicke's areas are involved in language production and comprehension, respectively.

fMRI offers higher spatial resolution than do lesion studies, and thus has enabled researchers to ask more specific questions. For example, do bilingual speakers use the same cortical areas for their native and second languages? The answer depends on the cortical area in question and the age at which an individual acquires the second language. For late bilinguals who were first exposed to the second language after 10 years of age, representations of the native and second languages in Broca's area map to adjacent but distinct loci (Figure 1–24A). In early bilinguals who learned both languages as infants, the two languages map to the same locus in Broca's area (Figure 1–24B). Thus, the age of language acquisition appears to determine how the language is represented in Broca's area. It is possible that after a critical period during development, native language has already consolidated a space in Broca's area, such that a second language acquired later must utilize other (adjacent) cortical areas. By contrast, the loci in Wernicke's area that represent the two languages are inseparable by fMRI even for late bilinguals (Figure 1–24C).

1.11 The brain uses maps to organize information

Thanks to the combination of anatomical, physiological, functional, and pathological studies on human subjects, we now have a detailed understanding of the gross organization of the human nervous system (see Figure 1–8A). This is complemented by experimental studies in mammalian model organisms, which

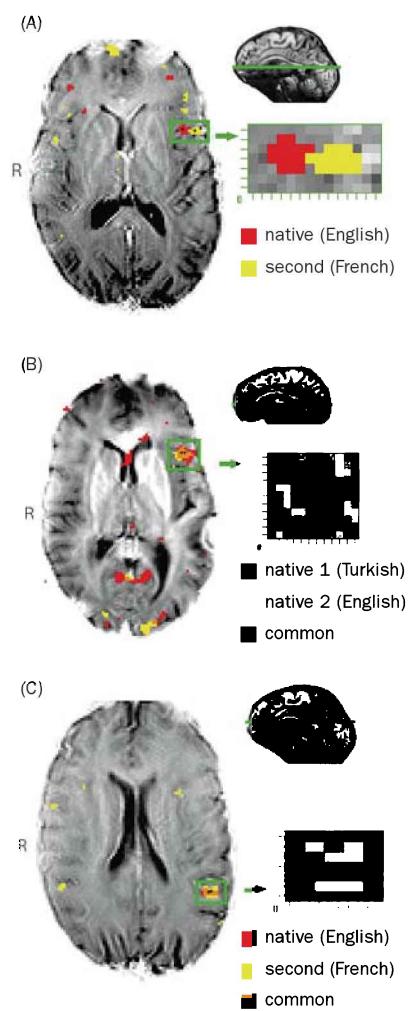


Figure 1–24 Representations of native and second languages as revealed by functional magnetic resonance imaging (fMRI). The detection of blood-flow signals associated with brain activity by fMRI provides a means for imaging the brain loci where native and second languages are processed. In the brain scans on the left side of the figure, green rectangles highlight language-processing areas in the left hemisphere; the highlighted areas are magnified on the right. In the miniature brain profiles located at top right, the green lines represent the section plane visualized in the scanned images. R, right hemisphere. **(A)** In a late bilingual, the two languages are represented in separate, adjacent loci within Broca's area. **(B)** In an early bilingual who learned both languages from infancy, the language representations in Broca's area overlap. **(C)** In Wernicke's area, the representations of native and second languages overlap regardless of when the second language was acquired; panels A and C came from the same late bilingual subject. (Adapted from Kim KH, Relkin NR, Lee K-M et al. [1997] *Nature* 388:171–174. With permission from Macmillan Publishers Ltd.)

share this gross organization (see Figure 1–8B). We will study the organization and function of many regions of the nervous system in detail in subsequent chapters.

An important organizational principle worth emphasizing at the very beginning is that the nervous system uses maps to represent information. We have already encountered this phenomenon in our earlier discussion of the auditory and visual maps that barn owls use to target their prey. Two striking examples of maps in the human brain are the **motor homunculus** and **sensory homunculus** (Figure 1–25). These homunculi ('little men') were discovered through the use of electrical stimulation during brain surgeries to treat epilepsy, as discussed in Section 1.10. For example, stimulation of cortical neurons in specific parts of the primary motor cortex elicits movement of specific body parts on the contralateral side. (Movement of the left side of the body is controlled by the right side of the brain and vice versa.) Systematic studies revealed a cortical **topographic map** corresponding to movement of specific body parts: nearby neurons in the motor homunculus control the movements of nearby body parts. This map is distorted in

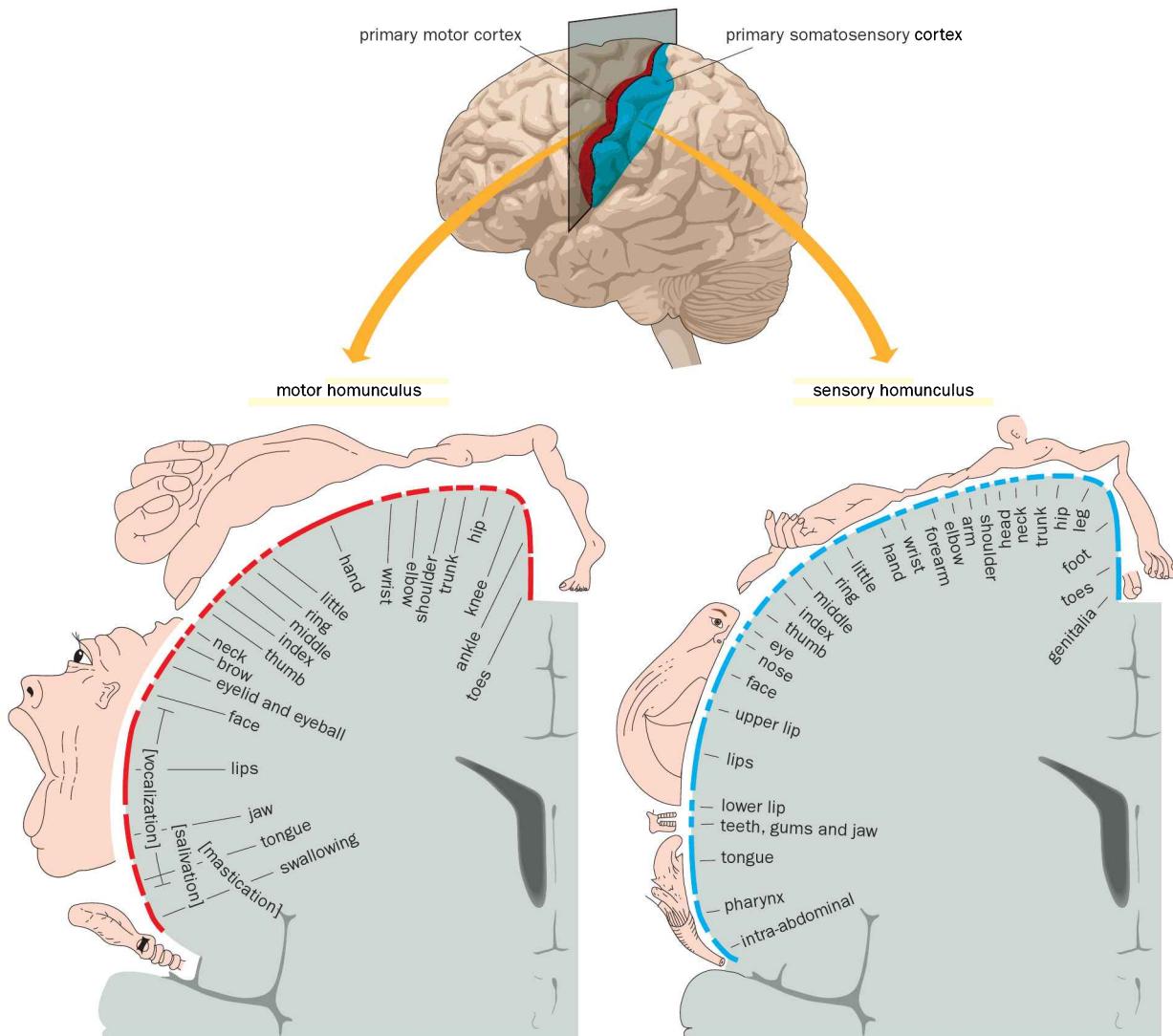


Figure 1–25 **Sensory and motor homunculi.** Top, the location in the brain of the primary motor cortex and the primary somatosensory cortex. Arrows indicate that sections along the plane with a 90° turn would produce the homunculi in the bottom panels. Bottom left, cortical neurons in the primary motor cortex control movement of specific body parts according to a topographic map. For example, neurons that control movement of lips and jaw are close together,

but are distant from neurons that control finger movement. Bottom right, cortical neurons in the primary somatosensory cortex represent a topographic map of the body. For example, neurons that represent touch stimuli on the lips, jaw, and tongue are in adjacent areas, distant from neurons that represent touch stimuli on the fingers. (Adapted from Penfield W & Rasmussen T [1950] *The Cerebral Cortex of Man*. Macmillan.)

its proportion. The hand, in particular the thumb, is highly overrepresented, as are the muscles surrounding the mouth that enable us to eat and speak (Figure 1–25, bottom left). These distortions reflect disproportional use of different muscles. As we will learn in Chapter 8, the motor homunculus is a simplified representation of a more complex organization of the motor cortex for movement control.

In the adjacent primary somatosensory cortex, there is an equivalent sensory homunculus. Stimulation of specific areas in the primary somatosensory cortex elicits sensations in specific body parts on the contralateral side (Figure 1–25, bottom right). Again, cortical neurons in adjacent areas represent adjacent body parts, forming a topographic map in the primary somatosensory cortex. This preservation of spatial information is all the more striking, considering that the cortical neurons are at least three synaptic connections away from the sensory world that they represent (see Figure 1–20). Obvious distortions are also present, such that some areas of the body (for example, the hand and especially the thumb) are overrepresented compared to other body parts (for example, the trunk). These distortions reflect differential sensitivities of different body parts to sensory stimuli such as touch. Interestingly, cortical neurons in the sensory and motor homunculi that represent the same body part are physically near each other, reflecting a close link between the two cortical areas in coordinating sensation with movement.

Neural maps are widespread throughout the brain. We will learn more about maps in the visual system (Chapter 4); the olfactory, taste, auditory, and somatosensory systems (Chapter 6); the motor system (Chapter 8); and the hippocampus and **entorhinal cortex** (part of the temporal cortex overlying the hippocampus), where maps are used to represent spatial information of the outside world (Chapter 10). We will also study how neural maps are established during development (Chapters 5 and 7).

1.12 The brain is a massively parallel computational device

The brain is often compared to the computer, another complex system that has enormous problem-solving power. Both the brain and the computer contain a large number of elementary units, the neurons and the transistors, respectively, which are wired into complex circuits to process information. The global architectures of the computer and the brain resemble each other, consisting of input, output, central processing, and memory (Figure 1–26). Indeed, the comparison between the computer and the brain has been instructive to both computer engineers and neurobiologists.

The computer has huge advantages over the brain in speed and precision of basic operations (Table 1–1). Personal computers nowadays can perform elementary arithmetic operations such as addition at a speed of 10^{10} operations per second. However, the speed of elementary operations in the brain, whether measured by the action potential frequency or by the speed of synaptic transmission across a chemical synapse, is at best 10^3 per second. Furthermore, the computer can represent quantities (numbers) with any desired precision according to the bits (binary digits, or 0s and 1s) assigned to each number. For instance, a 32-bit number has a precision of 1 in 2^{32} or 4.2×10^9 . Empirical evidence

Figure 1–26 Architectures of the computer and the nervous system.

(A) Schematic illustration of the five classic components of a computer: input (such as a keyboard or a mouse), output (such as a screen or a printer), memory (where data and programs are kept when programs are running), datapath (which performs arithmetic operations), and control (which tells datapath, memory, input, and output devices what to do according to the instructions of the program). Control and datapath together are also called the processor. (B) The nervous system can be partitioned in several different ways, one of which is shown here. In this four-systems model, the motor system controls the output of the nervous system (behavior). It is in turn controlled by three other systems: the sensory system that receives input from external environment, the cognitive system that mediates voluntary behavior, and the behavioral state system (such as wake/sleep) that influences the performance of all other systems. Arrows indicate extensive and often bidirectional connections among the four systems. As we will learn in Chapter 10, memory is primarily stored in the form of synaptic connection strengths of neural circuits in these systems. (A, adapted from Patterson DA & Hennessy JL [2012] Computer Organization and Design, 4th ed. Elsevier; B, adapted from Swanson LW [2012] Brain Architecture, 2nd ed. Oxford University Press.)

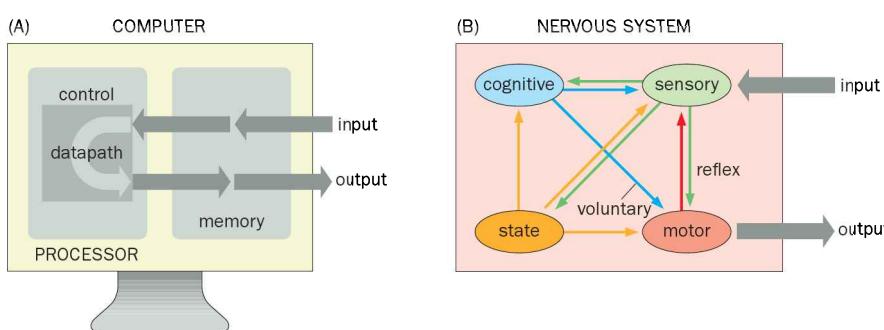


Table 1–1: Comparing the computer and the brain

Properties	Computer ¹	Human brain
Number of basic units	up to 10^9 transistors ²	$\sim 10^{11}$ neurons; $\sim 10^{14}$ synapses
Speed of basic operation	$10^{10}/\text{s}$	$<10^3/\text{s}$
Precision	1 in 4×10^9 for a 32-bit number	~ 1 in 10^2
Power consumption	10^2 watts	~ 10 watts
Processing method	mostly serial	serial and massively parallel
Input/output for each unit	1–3	$\sim 10^3$
Signaling mode	digital	digital and analog

¹ Based on personal computers in 2008.

² The number of transistors per integrative circuit has doubled every 18–24 months in the past few decades; in recent years the performance gains from this transistor growth has slowed, limited by energy consumption and heat dissipation.

(Data from von Neumann [1958] *The Computer and the Brain* 1st ed. Yale University Press; Patterson & Hennessy [2012] *Computer Organization and Design*, 4th ed. Elsevier).

suggests that most quantities in the nervous system have variability of at least a few percent due to biological noise, or a precision of 1 in 10^2 at best. What then enables the brain to outperform the computer in many complex tasks and to do so with a lower power consumption and impressive speed and precision—such as following the trajectory of a tennis ball after it is served at a speed as high as 72 m/s (160 miles per hour), moving to the optimal spot on the court, positioning the arm, and swinging the racket to return the ball in the opponent’s court, all within a few hundred milliseconds?

A notable difference between the computer and the brain is the methods by which information is processed within each system. Computer tasks are performed largely in **serial processing** steps; this can be seen by the way engineers program computers by creating a sequential flow of instructions, and by the fact that the operation of each basic unit, the transistor, takes a small number of inputs (1 to 3). For this sequential cascade of operations, high precision is necessary at each step because errors accumulate and amplify in successive steps. The brain also uses serial steps for information processing; in the tennis return example above, information flows from the eye to the brain and then to the spinal cord to control muscle contraction in the legs and arms. However, the nervous system also employs **massively parallel processing**, taking advantage of the large number of neurons and large number of connections each neuron makes. For instance, the moving tennis ball activates many photoreceptors in the eye, which transmit information to different kinds of bipolar and retinal ganglion cells (see Figure 1–16) as well as to inhibitory interneurons in the retina that we will learn about in Chapter 4; information regarding the location, direction, and speed of the ball is extracted by parallel circuits within two to three synaptic connections, and is transmitted in parallel by different kinds of retinal ganglion cells to the brain. Likewise, the motor cortex sends commands in parallel to control motor neuron activity and muscle contraction in the legs, the trunk, and the arms, such that the body and the arms are simultaneously well positioned for the incoming ball.

The massively parallel strategy is possible because each neuron collects inputs from and sends outputs to many other neurons—on average 10^3 for both inputs and outputs for a mammalian neuron. By using the divergent projection motif we discussed in Box 1–2, information from one neural center can be delivered to many parallel downstream pathways. At the same time, the convergent projection motif (see Figure 1–21A) allows many neurons that process the same information to send their inputs to the same postsynaptic neuron. While information represented by individual presynaptic neurons may be noisy, by taking the average of many presynaptic neurons, the postsynaptic neuron can represent the same information with much higher precision.

The computer and the brain also have similarities and differences in the signaling mode of their elementary units. The transistor utilizes **digital** signaling, which uses discrete values (0s and 1s) to represent information. The action

potential in neuronal axons is also a digital signal, since it has the all-or-none property; this enables reliable long-distance information propagation. However, neurons also utilize **analog** signaling, which uses continuous values to represent information. In non-spiking neurons, output is transmitted by graded potentials that can transmit more information than can action potentials (we will discuss this in more detail in Chapter 4). Neuronal dendrites also use analog signaling to integrate up to thousands of inputs. Finally, signals for interneuronal communication are mostly analog, as synaptic strengths are continuous variables.

Another important property of the nervous system at play in the tennis return example is that the strengths of synaptic transmission between presynaptic and postsynaptic partners can change in response to activity and experience, as we will study in greater detail in Chapter 10. Repetitive training enables the circuits to become better configured for the tasks being performed, resulting in greatly improved speed and precision.

Over the past decades, engineers have taken inspiration from the brain to improve computer design. For instance, the principles of parallel processing and use-dependent modification of circuits have both been incorporated into modern computers. At the same time, neurobiologists can enhance their understanding of the working of the nervous system and potential strategies it employs to solve complex problems by looking at the brain from an engineering perspective.

GENERAL METHODOLOGY

The development and utilization of proper scientific methodology is essential to advancing our knowledge of neurobiology. We devote the last chapter of this book (Chapter 13) to discussing important methods for exploring the brain. You are highly recommended to study the relevant sections of Chapter 13 when these methods are first introduced and referred to in Chapters 1-12. We conclude this chapter by highlighting a few general methodological principles that will be encountered throughout the book.

1.13 Observations and measurements are the foundations for discovery

At the beginning of this chapter, we noted that asking the right question is often a crucial first step in making important discoveries. A good question is usually specific enough that it can be answered with clarity in the framework of existing knowledge. At the same time, the question's answer should have broad significance.

Careful observation is usually the first step in answering questions. Observations can be made with increasing resolution using ever-improving technology. Our discussion in this chapter about the organization of the nervous system offers good examples. Cells were first discovered because of the invention of the light microscope. The elaborate shapes of neurons were first deciphered because of the invention of the Golgi staining method. The debate between the neuron doctrine and the reticular theory was finally settled with electron microscopy. Inventing new ways of observing can revolutionize our understanding of the nervous system.

Whereas observations can give us a qualitative impression, some questions can be answered only by quantitative measurement. For instance, in order to answer the question of how sensory stimuli are encoded by nerve signals, researchers needed to measure the size, shape, and frequency of the action potentials induced by varying stimulus strengths. This led to the fundamental discovery that stimulus strengths are encoded by the frequency of action potentials, but not by their size or duration. The development of new measurement tools often precedes great discoveries.

Observation and measurement go hand in hand. Observations can be quantitative and often form the basis for measurement. For example, electron microscopy

first enabled the visualization of the synaptic cleft. At the same time, it also permitted researchers to measure the approximate distance that a neurotransmitter must travel across a chemical synapse and estimate the physical size of the membrane proteins needed to bridge the two sides of a chemical synapse.

1.14 Perturbation experiments establish causes and mechanisms

While observation and measurement can lead to the discovery of interesting phenomena, they are often not adequate to investigate the underlying mechanisms. Further insight can be obtained by altering key parameters in a biological system and studying the consequences. We refer to these as **perturbation experiments**. Putting prisms on a barn owl is an example of a perturbation experiment. Artificial displacement of the visual map allowed scientists to measure the owl's ability to adjust its auditory map to match an altered visual map. We will encounter numerous perturbation experiments throughout the book.

Most perturbation experiments can be placed into one of the two broad categories referred to as 'loss-of-function' and 'gain-of-function.' In **loss-of-function experiments**, a specific component is taken away from the system. This type of experiment tests whether the missing component is *necessary* for the system to function. As an example, loss of speech caused by specific brain lesions in Broca's patients suggested that Broca's area is necessary for speech production. In **gain-of-function experiments**, a specific component is added to the system. Gain-of-function experiments can test whether a component is *sufficient* for the system to function in a specific context. As an example, electrical stimulations in epileptic patients indicated that activation of specific motor cortical neurons is sufficient to produce twitches of specific muscles. Both loss- and gain-of-function experiments can be used to deduce the causal relationships between components in biological processes.

Originating from the field of genetics, the terms 'loss-of-function' and 'gain-of-function' refer to the deletion or misexpression, respectively, of a specific gene to test its function in a biological process. These experiments are extremely powerful because genes are the basic units for regulating many biological processes, including neurobiological processes. In addition, genetic perturbations can be performed with high precision in many model organisms (see Sections 13.6–13.11). Indeed, we will introduce many examples of gene perturbation experiments that have shed light on the underlying mechanisms of a variety of neurobiological processes.

As the lesion and electrical stimulation examples discussed above illustrate, the concept of loss- and gain-of-function perturbation can be broadened beyond genes. In contemporary neuroscience, a central issue is the analysis of neural circuit function in perception and behavior, and here single neurons or populations of neurons of a particular type are the organizational and operational units. To assess the function of specific neurons or neuronal populations in the operation of a circuit, tools have been developed that can conditionally silence their activity (loss-of-function) or artificially activate them (gain-of-function) with high spatiotemporal precision (see Sections 13.10–13.12 and 13.23–13.25). Given that neurons can participate in neural circuits in a myriad of different ways (see Box 1–2), precise perturbation experiments are crucial in revealing the mechanisms by which neural circuits operate and control neurobiological processes of interest. These experiments also help establish causal relationships between the activities of specific neurons and the neurobiological processes they control.

With these basic concepts and general methodologies in hand, let us begin our journey!

SUMMARY

In this chapter, we have introduced the general organization of the nervous system and some fundamental concepts of neurobiology, framing these topics from a historical perspective. Neurons are the basic building blocks of the nervous system. Within most vertebrate neurons, information—in the form of membrane potential changes—flows from dendrites to cell bodies to axons. Graded potentials in dendrites are summed at the junction between the cell body and the axon to produce all-or-none action potentials that propagate to axon terminals. Neurons communicate with each other through synapses. In chemical synapses, presynaptic neurons release neurotransmitter in response to the arrival of action potentials, and postsynaptic neurons change their membrane potential in response to neurotransmitter binding to their receptors. In electrical synapses, ions directly flow from one neuron to another through gap junctions to propagate membrane potential changes. Neurons act in the context of neural circuits, and form precise connections with their synaptic partners to process and propagate information within circuits. Neural circuits in different parts of the brain perform distinct functions that range from sensory perception to motor control, and the nervous system employs a massively parallel computational strategy to enhance the speed and precision of information processing. In the rest of the book, we will expand our studies of these fundamental concepts in the organization and operation of the nervous system.

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