Learning and Memory

From Brain to Behavior

THIRD EDITION

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The Neuroscience of Learning and Memory

IN THE MIDST OF A NEIGHBORHOOD BASEBALL GAME, a ball hit Orlando Serrell in the head so hard that it knocked him to the ground. At the time, he was only 10 years old, and like most boys who take a hit while playing with peers, he walked it off and eventually went back to the game. This seemingly innocuous incident proved anything but typical, however. Sometime after the hit, Orlando discovered an amazing ability to remember the day of the week on which any date fell that occurred after the fateful game, as well as what the weather was like on most of those days, without making any conscious effort to memorize this information or perform calculations with dates. Orlando's case is not unique but is an instance of a rare condition called *acquired savant syndrome* (Treffert, 2009). Chapter 1 described Clive Wearing, who lost many of his memory abilities after part of his brain was destroyed. Unlike Clive, individuals with acquired savant syndrome actually gain prodigious memory capacities as the result of brain injury. The startling implication of this phenomenon is that at least some human brains (and perhaps all) appear to have a much greater capacity for storing and recalling memories than people typically exhibit. If humans have hidden learning and memory capacities, might other animals also possess capacities of which we are currently unaware? If brains have such capacities, then why can't all individuals take full advantage of them? Might it be possible to develop neural technologies that enable a person to better encode and recall specific information or to erase memories of episodes one would prefer to forget?

The story of how scientists explore such questions, and identify the biological factors that determine what an individual remembers or forgets, is the story of the neuroscience of learning and memory. Although scientists still have a long way to go in understanding how nervous systems work, they are compiling

LEARNING AND MEMORY IN EVERYDAY LIFE

Top Five Tips for Faster Forgetting

Chapter 1 provided 10 tips for how you can change your behavior to improve your memory. In case you are more interested in erasing memories than retaining them (wasting time is fun!), you can also modify your brain function to improve your forgetting. Here's what you do.

1. *Don't sleep.* People who don't get enough sleep are less able to concentrate during the day, which makes it harder for them to encode new memories and retrieve old ones. Sleepy brains work worse.
2. *Stress out.* Stress generally interferes with recall. So, if you want to make retrieving information particularly troublesome, just keep fixating on trying to remember things you can't, until frustration overcomes you.
3. *Overextend yourself.* The more things you try to keep in mind simultaneously, the greater the chance you'll forget a bunch of them. So put aside all your note-taking devices—your pens, pads, computers, and iPhones—if you really want to maximize your loss.
4. *Deprive your senses.* The more impoverished your sensory inputs, the less likely you will encode facts, events, and skills well enough to recall them later. Wear headphones, shades, and oven mitts. Minimize the brain activity.
5. *Be apathetic.* Nothing is more forgettable than something you couldn't care less about. Just keep chanting inside your head, "Whatever . . . Whatever . . . Whatever," and you can easily avoid the kinds of emotionally triggered brain states that make memories stick.

fascinating information about the brain's structure and functioning and the ways it contributes to learning and memory. New imaging and sensing technologies allow researchers to observe healthy human brains as they form and retrieve memories, while new techniques for animal research allow researchers to measure and manipulate neural changes during learning. Insights into the neural mechanisms of learning and memory can help you to understand how your actions may impact your own attempts to learn, remember, and in some cases forget the materials you study (for some ideas, see "Learning and Memory in Everyday Life," on this page).

2.1 Structural Properties of Nervous Systems

neuroscience. The study of the brain and the rest of the nervous system.

Researchers in the field of **neuroscience**—the study of the brain and the rest of the nervous system—overwhelmingly believe that the brain is the seat of learning and memory. This was not always the prevailing opinion. When ancient Egyptians mummified a body, they first removed the organs they considered important, preserving them in special airtight jars—but they discarded the brain. Many centuries later, Aristotle, one of the most empirically oriented philosophers in history, argued that the brain served primarily to cool the blood. However, observations over the centuries since Aristotle's time have convinced scientists that brain activity controls behavior and, by extension, the changes in behavior associated with learning and memory.

Historically, most early studies of learning and memory focused on observable behavior rather than on the brain and how it functions (Chapter 1). This is not because early learning and memory researchers were oblivious to the importance of the brain. Ivan Pavlov designed all of his behavioral experiments to answer questions about how the brain works. John Watson, the originator of behaviorism, started out studying how developmental changes in neural structures

correlate with developmental changes in learning abilities. B. F. Skinner, perhaps the most famous behaviorist of the twentieth century, began his career as a physiologist. Why, then, did these researchers place so much emphasis on behavior and so little emphasis on the role of the brain?

Part of the answer is that brains are among the most complex structures in nature. Even as recently as 50 years ago, the complexity of the neural functions required for most learning tasks seemed incomprehensible. As new technologies became available, however, the study of brain function became more manageable. Today, aspects of brain function that previously were inaccessible are being measured daily in laboratories and medical institutions around the world. These new technologies have dramatically increased the number and productivity of studies exploring the neural substrates of learning and memory.

nervous system. An organism's system of tissues specialized for distributing and processing information.

neuron. A type of cell that is specialized for information processing.

central nervous system (CNS). The part of the vertebrate nervous system consisting of the brain and spinal cord.

peripheral nervous system (PNS). The part of the nervous system that carries information from sensory receptors to the central nervous system and carries commands from the CNS to muscles.

What Brains Are Like

The brain is just one—albeit very important—component of a collection of body organs called the **nervous system**, the organ system devoted to the distribution and processing of signals that affect biological functions throughout the body. The tissues that are specialized for accomplishing these tasks include cells called **neurons**, which collect incoming signals from the sensory organs of the system (leading to sight, taste, smell, touch, and sound) and from the rest of the body (indicating such conditions as hunger and sleepiness), process these signals, and react to them by coordinating the body's responses (such as muscle movement and activity of internal organs).

In vertebrates, the nervous system can be divided into two parts: the central nervous system and the peripheral nervous system. As its name suggests, the **central nervous system (CNS)** is where many of the events responsible for learning and memory take place: the CNS is made up of the brain and the spinal cord (Figure 2.1). The **peripheral nervous system (PNS)** consists of nerve fibers that connect sensory receptors (for example, visual receptors in the eye or touch receptors in the skin) to the CNS and of other fibers that carry signals from the CNS back out to the muscles and organs. Most of these fibers pass through the spinal cord, but a few—such as those from the light receptors in your eyes and those that activate the muscles controlling eye movements—travel directly to the brain without first making connections in the spinal cord.

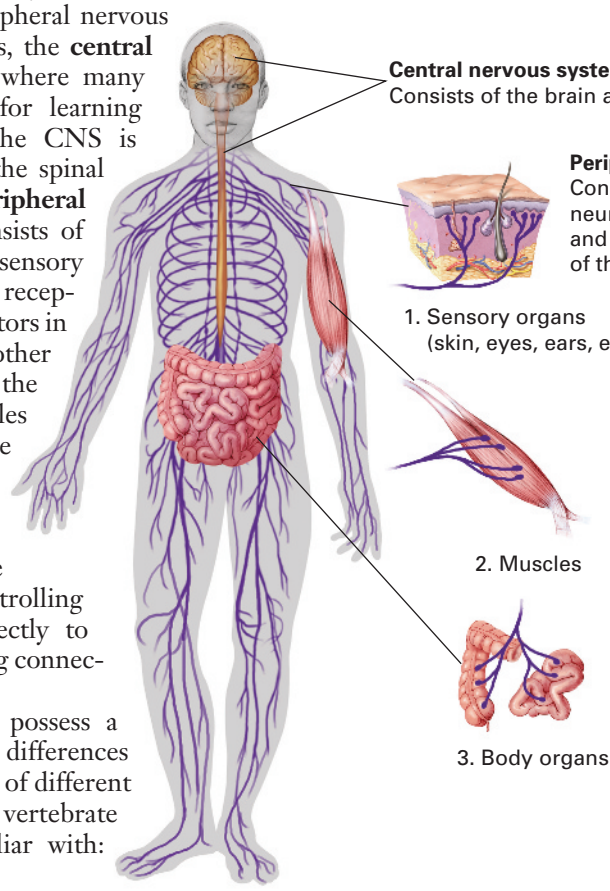


Figure 2.1 Nervous system components Every vertebrate has a central nervous system (CNS) and a peripheral nervous system (PNS). The CNS consists of the brain and spinal cord. The PNS consists of motor and sensory neurons that transmit signals between the CNS and the rest of the body: (1) sensory receptors in the skin, eyes, ears, and so on provide sensory inputs to the CNS; (2) motor fibers deliver directives from the CNS to muscles; (3) PNS fibers from the CNS regulate organs and glands.

Although all vertebrates possess a CNS and PNS, there are big differences between the nervous systems of different species. Let's start with the vertebrate you're probably most familiar with: the human.

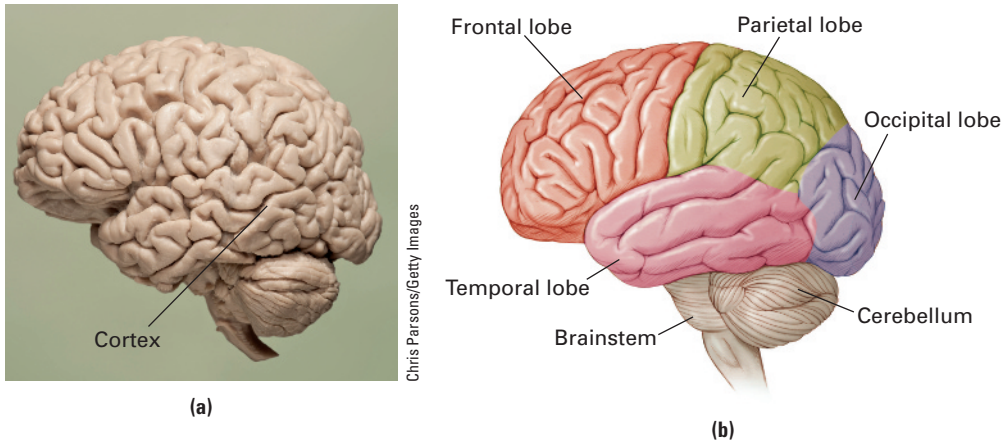


Figure 2.2 The visible surface of a human brain
(a) A photograph of a human brain. (b) In each brain hemisphere, the visible cerebral cortex is divided into four principal areas: frontal lobe, parietal lobe, occipital lobe, and temporal lobe. Below the cerebral cortex are the cerebellum and brainstem. The brainstem connects the brain to the spinal cord.

cerebral cortex. The brain tissue covering the top and sides of the brain in most vertebrates; involved in storage and processing of sensory inputs and motor outputs.

frontal lobe. The part of the cerebral cortex lying at the front of the human brain; enables a person to plan and perform actions.

parietal lobe. The part of the cerebral cortex lying at the top of the human brain; important for processing somatosensory (touch) information.

temporal lobe. The part of the cerebral cortex lying at the sides of the human brain; important for language and auditory processing and for learning new facts and forming new memories of events.

occipital lobe. The part of the cerebral cortex lying at the rear of the human brain; important for visual processing.

cerebellum. A brain region lying below the cerebral cortex in the back of the head. It is responsible for the regulation and coordination of complex voluntary muscular movement, including classical conditioning of motor-reflex responses.

brainstem. A group of structures that connects the rest of the brain to the spinal cord and plays key roles in regulating automatic functions such as breathing and body temperature.

The Human Brain

The **cerebral cortex**, the tissue covering the top and sides of the brain in most vertebrates, is by far the largest structure of the human brain (Figure 2.2a). The word *cortex* is Latin for "bark" or "rind," reflecting that the cortex, although about the size of the front page of a newspaper if spread out flat, is only about 2 millimeters thick. To fit inside the skull, the cerebral cortex is extensively folded, much like a piece of paper crumpled into a ball. In humans, as in all vertebrates, the brain consists of two sides, or *hemispheres*, that are roughly mirror images of each other, so brain scientists talk about the cortex in the "left hemisphere" or the "right hemisphere." In each hemisphere, the cortex is divided further into the **frontal lobe** at the front of the head, the **parietal lobe** at the top of the head, the **temporal lobe** at the side of the head, and the **occipital lobe** at the back of the head (Figure 2.2b). The term *lobe* refers to the fact that these regions are anatomically distinct. The individual lobes got their somewhat odd names from the names of the skull bones that cover them. If you have trouble memorizing these four terms, remember: "*F*rontal is *F*ront, *P*arietal is at the *P*eak, *T*emporal is behind the *T*emples, and the *O*ccipital lobe is *O*ut back." Subregions within each lobe are associated with a wide variety of perceptual and cognitive processes. For example, your frontal lobe helps you to plan and perform actions, your occipital lobe allows you to see and recognize the world, your parietal lobe enables you to feel the differences between silk and sandpaper, and your temporal lobe makes it possible for you to hear and to remember what you've done. We will discuss the functional roles of cortical subregions in greater detail throughout this book, and knowing the names and locations of the different lobes will help you to keep track of what is happening where in your brain.

Sitting behind and slightly below the cerebral cortex is the **cerebellum** (Figure 2.2b). The cerebellum contributes to the coordination of sensation and movements and is thus especially important for learning that involves physical action. At the base of the brain is the aptly named **brainstem** (Figure 2.2b). The brainstem is a collection of structures connecting the brain to the spinal cord and playing key roles in the regulation of automatic functions, such as breathing and the regulation of body temperature.

Other brain structures, buried under the cerebral cortex, are not visible in photographs such as that shown in Figure 2.2a. You'll learn about many of these structures later in the book; for now, we'll just introduce a few that are especially important for learning and memory (Figure 2.3).

First, near the center of the brain lies the *thalamus*, a structure that receives various sensory signals (associated with sight, sound, touch, and so forth) and that connects to many cortical and subcortical regions. You can think of the thalamus as a gateway through which almost all sensory signals can affect brain activity. Sitting near the thalamus are the *basal ganglia*, a group of structures important for planning and producing skilled movements such as throwing a football or juggling. The *hippocampus* lies a little farther away, inside the temporal lobe; it is thought to be important for learning new facts (say, the capital of France) or remembering autobiographical events (what you did last summer). Sitting at the tip of the hippocampus is a group of cells called the *amygdala*; this little brain region is important for emotional memories. If you remember the happiest—or saddest—day of your life, it is probably because your amygdala was particularly active at the time, adding emotional strength to those memories. Because you have two hemispheres, you actually have duplicates of each of these structures. For example, you have a left hippocampus and a right hippocampus, and a left amygdala and a right amygdala.

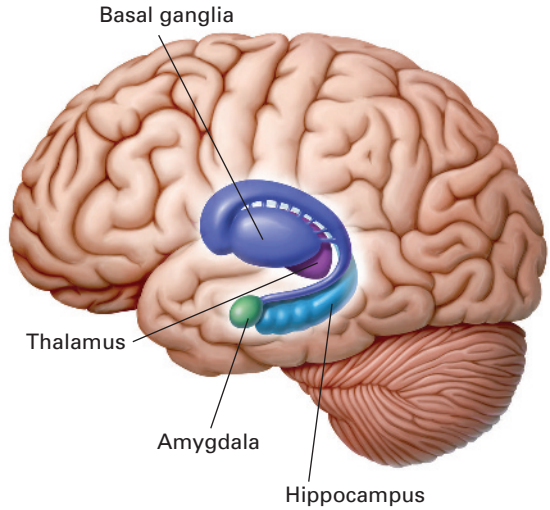


Figure 2.3 Brain regions known to contribute to learning and memory Lying near the center of the human brain, the basal ganglia, thalamus, hippocampus, and amygdala all contribute to learning and memory in different ways.

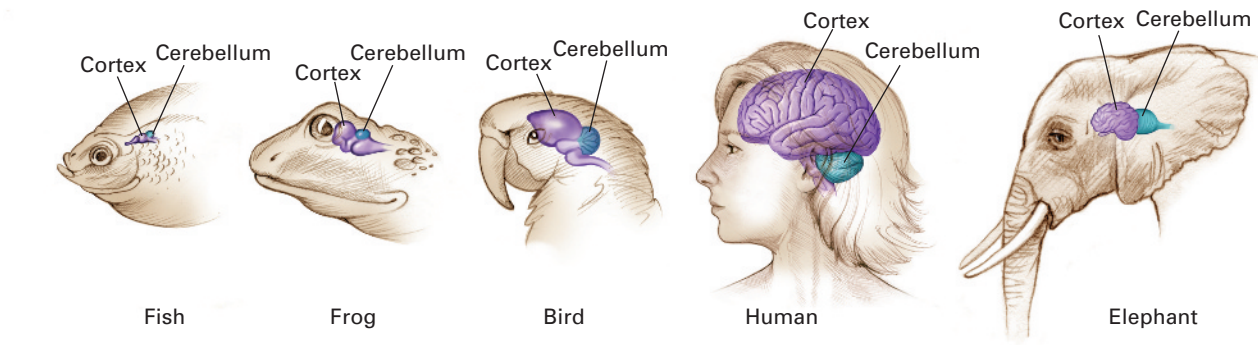
Scientists are only beginning to understand what these brain areas do and how they relate to learning and memory, but it is becoming increasingly clear that it's a mistake to think of the brain as a single organ, like a liver or a kidney. Instead, the brain is a society of "experts," with each region making its own specialized contribution to what we do and what we think.

Comparative Neuroanatomy

In spite of the wide differences in nervous systems from species to species, much of what is known about the neural bases of learning and memory comes from studies of animals other than humans. Many aspects of a rat brain, a monkey brain, or even an insect brain are similar enough to a human brain to have made this possible (as predicted by Darwin's theory of natural selection, described in Chapter 1). The study of similarities and differences between organisms' brains is called *comparative neuroanatomy*. Comparative neuroanatomical studies provide a foundation for understanding how brain structure and function relate to learning and memory abilities.

The brains of vertebrate species are similar in that all have a cerebral cortex, a cerebellum, and a brainstem; all vertebrate brains are also similarly organized into two hemispheres. Figure 2.4 shows the brains of some representative vertebrate species. In general, bigger animals have bigger brains. It might seem that increasing brain size should go hand in hand with increased capacity:

Figure 2.4 Comparative anatomy of the brains of several vertebrate species All vertebrate brains have two hemispheres and a recognizable cortex, cerebellum, and brainstem, but species differ in the relative volumes of these areas. In mammals (such as the human) and birds, the cortex is much larger than the cerebellum; in fish and amphibians (such as the frog), the cortex and cerebellum are closer in size.

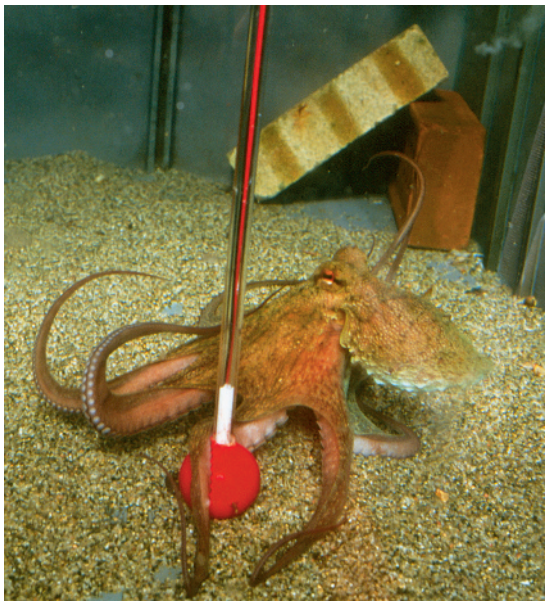


human brains are bigger than frog brains, and humans seem to be able to learn things frogs can't. But elephant brains are larger than human brains, and elephants can't learn to read and write, build cities, or study calculus. So, just as birds with larger wings are not necessarily better at flying than smaller birds, animals with larger brains are not necessarily better learners than other animals. In general, scientists don't yet fully understand the relationship between brain size and functional capacity. Studies of intelligence in humans suggest that differences in the size of certain subregions in the frontal and parietal lobes do predict differences in performance on intelligence tests (Jung & Haier, 2007), indicating that it is not overall brain size that matters but how different brain parts are structured (Mercado, 2008).

Aside from differences in overall brain volume, different species have different proportions of cerebral cortex. In humans, the cerebral cortex takes up a much larger percentage of total brain volume than it does in, say, frogs. Whereas the large human cortex has to be folded up to fit inside the human skull, the frog cortex can fit quite comfortably in its skull without wrinkling. The relative size of the human cortex is intriguing because the cerebral cortex is associated with functions such as language and complex thought—the very things that seem to distinguish humans from other animals. And in fact, other species with a relatively large cortex—including chimpanzees, dolphins, and, yes, elephants—are often those that we associate with greater ability for abstract thought, problem solving, and remembering the details of past events.

Only vertebrates have both a CNS and a PNS. Some invertebrates—the octopus and the bee, for example—have a recognizable brain, but these brains are organized very differently from vertebrate brains. Much of the octopus "brain" is distributed in various parts of its body, particularly inside its rubbery legs. Yet the octopus is a remarkably capable learner: it can learn to find its way through a maze and to open a jar to get at the food inside. It even shows signs of social learning, that is, learning from watching another octopus's behavior. In one study, researchers trained some octopuses to grab the white ball when presented with a choice between a white and a red one. Other, untrained octopuses were then allowed to watch the trained octopuses make their selection. Later, when the observer octopuses were offered the two balls, they promptly grabbed the white one—just as they had seen the trained octopuses doing (Fiorito, Agnisola, d'Addio, Valanzano, & Calamandrei, 1998). Such social learning was once believed to be exclusive to "higher" animals, such as humans, dolphins, and chimpanzees. But we now know that an octopus, with a decentralized brain, can learn from observing others, too.

When an invertebrate such as the octopus learns about a novel object, is the learning happening in its head, or is it happening in one or more of its legs?



Mauro Fermariello/Science Source

Other invertebrates, such as worms and jellyfish, have no recognizable brains at all. These animals have neurons that are remarkably similar to vertebrate neurons, but the neurons are few in number and are not organized into a centralized structure like a brain. For example, microscopic worms known as nematodes (including the species that infects pigs and then humans who eat the pigs, causing trichinosis) have 302 individual neurons, compared with a few hundred million in the octopus and about 100 billion in the human. Nematode neurons are organized into a "nerve net" that is similar to a vertebrate PNS but with no central processing area. Yet these little organisms can learn to approach tastes or odors that predict food and to avoid tastes and odors that predict the absence of food (Rankin, 2004). Not bad for a creature without a brain.

Studies of invertebrate nervous systems have been particularly rewarding because of their very simplicity. For example, because a nematode has such a small number of neurons, scientists are able to map out the entire set of connections in its nervous system in a way not yet possible for a human brain or even a rat brain. Many of the important insights into human brains and human learning have come from studying how invertebrates learn and remember.

Neurons

Neurons are the building blocks of the nervous system. Some act as sensory receptors (such as those in the eyes, ears, and tongue that respond to visual, auditory, and taste stimuli), and some transmit signals from the spinal cord to the muscles. In vertebrates, many neurons are centralized in the brain. Neurons are capable of changing their function and modifying the way they respond to incoming signals. These changes, some of which we examine in Section 2.3, are thought to be the basis of learning in the brain.

The prototypical neuron has three main components: (1) **dendrites**, which are input areas that receive signals from other neurons; (2) the **cell body**, or **soma**, which integrates signals from the dendrites; and (3) one or more **axons**, which transmit signals to other neurons (Figure 2.5). For the most part, neural activity flows in one direction, from dendrites to axons.

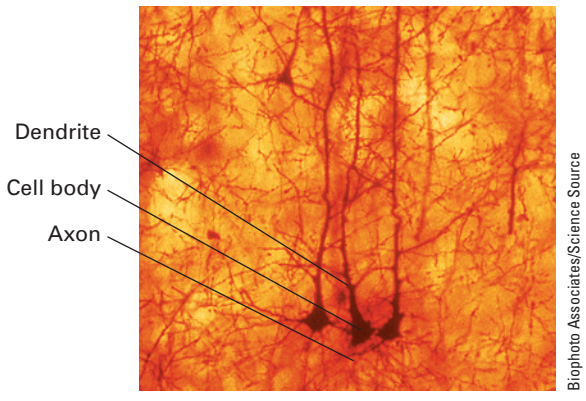
It is convenient to talk about a "prototypical neuron," but in reality neurons, like brains, come in a wide array of shapes and sizes. For example, *pyramidal cells* are neurons with pyramid-shaped cell bodies (shown in Figure 2.5a); *stellate cells* have star-shaped cell bodies. Some neurons have a single main axon, some have two, and some have many. Neurons known as *interneurons*, which connect two or more neurons, have short axons or no axons at all. The neurons that carry signals from the spinal cord to the feet have axons that stretch a meter or more in humans. The various shapes and sizes of different neurons undoubtedly contribute to their function. But, in many cases, neuroscientists do not know the specific advantages that a particular shape or size provides.

dendrite. Extension of a neuron that is specialized to receive signals from other neurons.

cell body. The central part of the neuron that contains the nucleus and integrates signals from all the dendrites; also known as the soma.

soma. The central part of the neuron that contains the nucleus and integrates signals from all the dendrites; also known as the cell body.

axon. The output extension of a neuron, specialized for transmitting information to other neurons or to muscles.



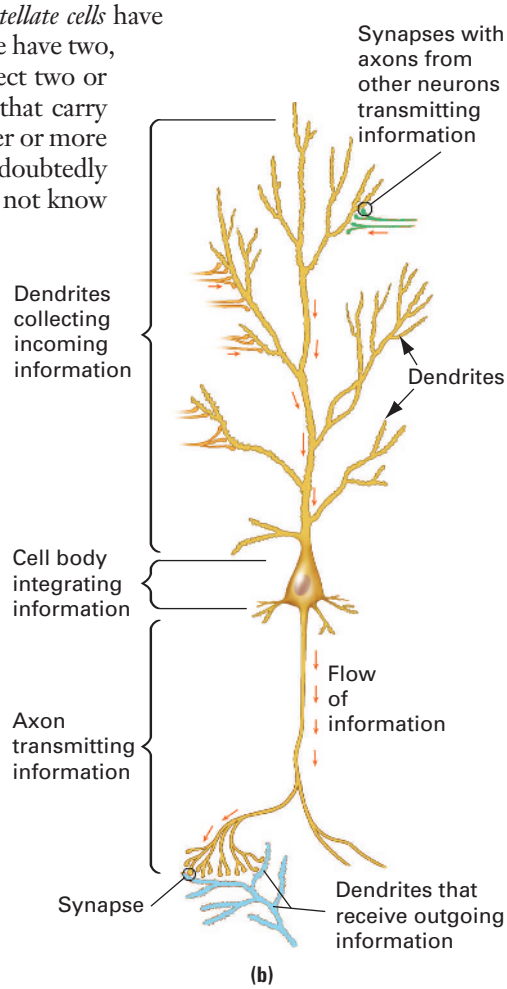


Figure 2.5 Neurons, the building blocks of brains
(a) Brain tissue, stained to make neurons evident and photographed through a powerful microscope. The pyramid-shaped cell bodies and interconnecting branches of several neurons are visible. (b) The prototypical neuron has three main components: dendrites for monitoring the activity of other neurons, a cell body (soma) that integrates incoming signals, and one or more axons that transmit signals to other neurons. Neural activity flows mainly from dendrites to axon(s).

glia. A type of cell that provides functional or structural support to neurons.

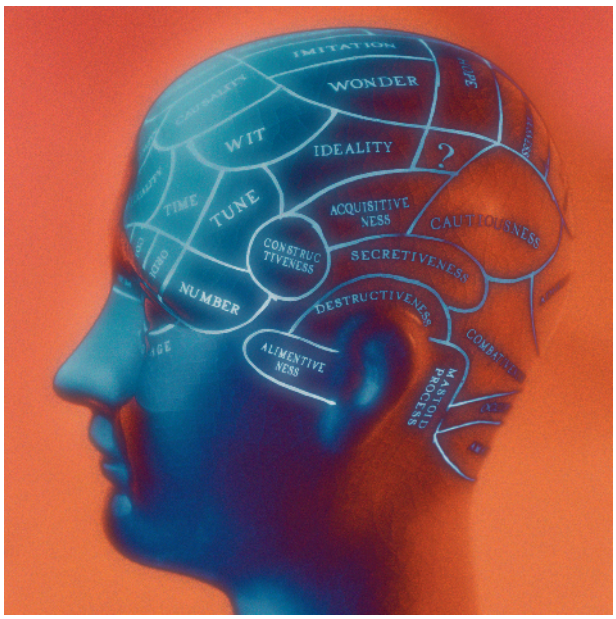
Neurons are not the only kind of cell in the brain; they are far outnumbered by **glia**, cells that provide functional and structural support to neurons. *Astrocytes* are glia that line the outer surface of blood vessels in the brain and may help in the transfer of oxygen and nutrients from the blood to neurons. Glia called *oligodendrocytes* wrap the axons of nearby neurons in *myelin*, a fatty substance that insulates electrical signals transmitted by neurons, speeding the transmission of signals down the axon. Glia are as important as neurons for normal brain (and overall central nervous system) function. For example, multiple sclerosis is a disease in which the myelin coating of axons degenerates; this interferes with neural function, leading to jerky muscle movements and impaired coordination, as well as problems with vision and speech. Glia may also directly contribute to certain learning mechanisms. Even so, most neuroscientists who study the neural bases of learning and memory focus their efforts on understanding neurons: how they control behavior, and how they change during learning.

Observing Learning-Related Changes in Brain Structure

phrenology. A field of study that attempted to determine mental abilities by measuring head shape and size.

In the late 1800s, Franz Joseph Gall (1758–1828), a German anatomist and physiologist, pioneered the idea that different areas of the brain are responsible for different behaviors and capabilities. In addition, he reasoned that differences in character or ability should be reflected in differences in the size of the corresponding parts of the brain: people with a special skill for learning language must have a larger-than-average part of the brain associated with speech; people with better memories must have an overgrown memory area in the brain. Gall assumed that these differences in brain areas would be reflected in the shape of the skull, and he concluded that it should be possible to tell which areas of a person's brain were enlarged—and, thus, what abilities and personality traits that person would display—by examining bumps in the person's skull. Gall and his colleagues pursued a systematic study they called **phrenology**, in which they carefully measured the size and shape of many individuals' skulls and compared those measurements with the individuals' personalities and abilities (Gall & Spurzheim, 1810).

Phrenology maps attributed various aspects of cognition, personality, and memory abilities to variations in the sizes of different regions of a person's brain as indicated by bumps on the person's skull. How is the fundamental flaw of phrenology reflected in this image?



Chad Baker/Ryan McVay/Getty Images

Phrenology captured the public imagination. The approach was quickly taken over by quacks, who found various ways of making the idea pay. There was another, even more serious problem than the enthusiastic overuse of phrenology, however. It was that Gall's fundamental premise was wrong. Bumps on the skull do not imply bulges in the underlying brain. Gall did not discover this flaw because he had no way to examine the brain of a living person. It would be nearly 200 years before technology advanced to the point where scientists could see inside the skull of a healthy, living person and begin to identify brain structures that determine what individuals can learn and remember.

Structural Neuroimaging in Humans

Today, several technologies are available that allow physicians to see a living person's brain without causing damage or malfunction. Collectively, these modern techniques for creating pictures of anatomical structures within the brain are called

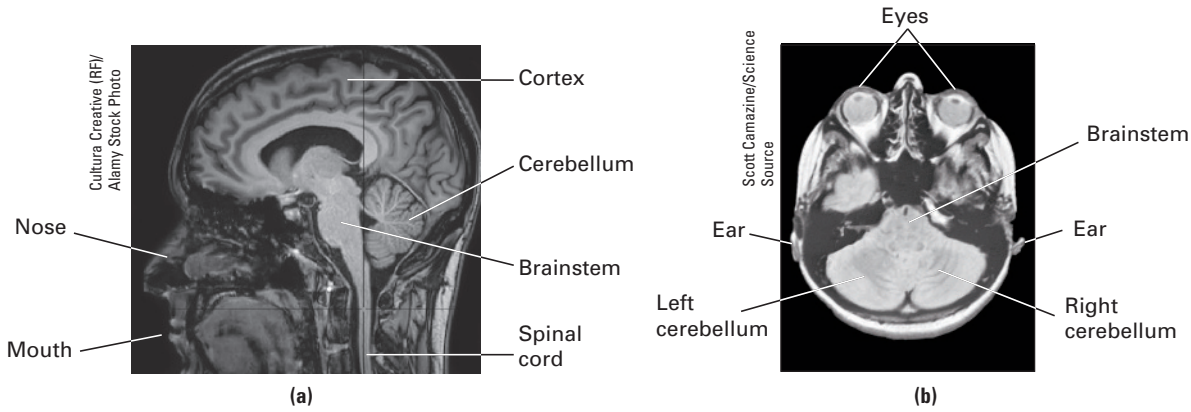


Figure 2.6 MRI images
(a) This brain image measured near the center of the head shows a cross section through cortex, cerebellum, brainstem, and an upper portion of spinal cord, as well as nose and mouth cavities. (b) An image measured at the level of the eyeballs (visible at the top of the image) contains little cortex (since the position is so far down in the person's head) but captures the low-hanging cerebellum.

structural neuroimaging, brain imaging, or "brain scanning." The brain scans produced by these methods show the size and shape of brain areas and also brain **lesions**, areas of damage caused by injury or illness.

Currently, brain images are most often collected from people through **magnetic resonance imaging (MRI)**, in which changes in magnetic fields are used to generate images of internal structure. MRI employs an extremely powerful magnet, usually constructed like a giant tube. The person lies on a pallet that slides into the tube, and magnetic changes are induced in the brain tissues, which are then allowed to return to normal. During this latter phase, a computer collects the different signals emitted by different tissues and uses them to generate images that look like photographs of a sliced brain. For example, Figure 2.6a shows an image comparable to what you would see if someone's head were sliced in half (minus the spewing blood), revealing a cross section of cerebral cortex, cerebellum, and brainstem, as well as some facial structures. An image measured at the level of the eyeballs, as in Figure 2.6b, shows a different cross section.

Recently, a new type of MRI called **diffusion tensor imaging (DTI)** was developed that can measure the diffusion of water in brain tissue, permitting bundles of axons throughout the brain—the so-called white matter—to be imaged. DTI is better than conventional MRI at visualization of groups of axons, so it's particularly useful for physicians trying to assess diffuse brain injury, as well as diseases such as multiple sclerosis that specifically target axons. Researchers also use DTI to study how different regions in the brain interact, by studying the pathways between them.

Structural neuroimaging provides a way not only to directly observe physical properties of a live person's brain but also *to track changes in those properties over time*. These include changes that might occur as a function of aging, injury, or disease, as well as gross structural changes produced by learning experiences. In Chapter 7, on skill memories, we discuss recent structural neuroimaging work showing that learning to juggle leads to changes in the amount of cortical tissue. Structural images of human brains are also critical for analyzing and interpreting changes in brain *function* that occur with learning, a topic we discuss in greater detail below.

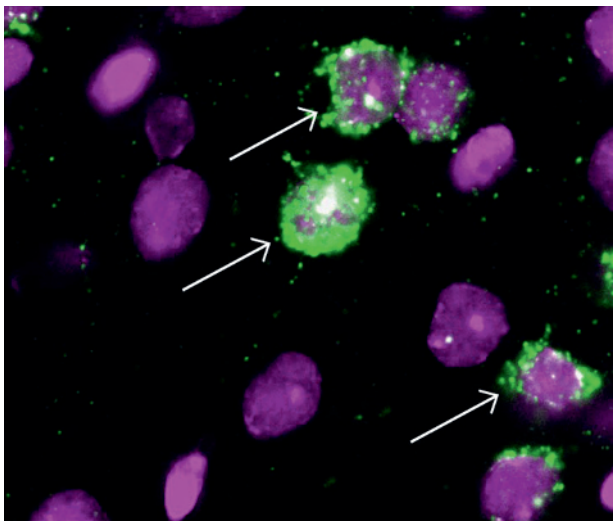
It is easy to confuse structural neuroimaging, which shows what brains are physically like, with a different kind of imaging known as *functional neuroimaging*, which is presented in Section 2.2 and shows what brains are *doing* at the time of imaging. Both types of neuroimaging can reveal changes associated with learning, and we will present examples of both throughout the following chapters. Whenever you see an image in which patches of color are superimposed on a picture of a brain, the first thing you should ask yourself is, are these colored regions showing me changes in structure, or do they show changes in brain activity?

structural neuroimaging. Techniques (such as MRI) for creating images of anatomical structures within the living brain.

lesion. Damage caused by injury or illness.

magnetic resonance imaging (MRI). A method of structural neuroimaging based on recording changes in magnetic fields.

diffusion tensor imaging (DTI). A type of MRI that measures the diffusion of water in brain tissue, permitting bundles of axons throughout the brain to be imaged.



Sakaguchi and Hayashi: Catching the engram: strategies to examine the memory trace. Molecular Brain 2012 5:32.

Techniques for imaging neurons in brains make it possible to visualize structural changes that occur during learning. Do you think the changes shown here in green occurred in the dendrites, soma, or axons of these neurons?

Effects of Learning

Experimental studies with animals permit even more detailed measures of learning-related structural changes. Chemicals have been developed that essentially dye neurons that have recently undergone structural changes, making it possible to map out the number and distribution of neurons that have changed as a function of specific learning experiences. For some imaging techniques, the brain tissue has to be bathed in the chemicals, and the dyed neurons are only visible through a microscope, so the brain must be removed from the animal soon after the learning occurs. For other techniques, however, it is possible to collect images of single neurons and even individual dendrites in living animals. These methods are most often employed in studies of learning that use rodents, small birds, or small invertebrates as subjects.

Early studies of brain structure in rats found that simply providing young rats with more opportunities for learning could lead to visible changes in their neurons. Researchers housed one group of rats in an **enriched environment**, meaning an environment where there was plenty of sensory stimulation and opportunity to explore and learn. For the rats, this meant a large cage filled with toys to play with and other rats with whom to socialize. A second group of rats lived in standard laboratory housing, each rat isolated in a small chamber that contained nothing but a drinking spout and food cup. The results? The rats housed in the enriched environment showed better maze learning than the rats kept in standard laboratory housing (Rosenzweig, 1984; Renner & Rosenzweig, 1987).

enriched environment. An environment that provides sensory stimulation and opportunities to explore and learn; for a rat, this may mean housing in a large cage with many toys to play with and other rats to socialize with.

These increased learning capacities are associated with structural changes in neurons. Rats raised in an enriched environment have cortical neurons with more and longer dendrites than their experience-impoverished counterparts (Figure 2.7). The dendrites of rats in the enriched environment also have more connections with other neurons (Globus, Rosenzweig, Bennet, & Diamond, 1973; Greenough, West, & DeVoogd, 1978). These neural changes occur quickly: as few as 60 days of housing in an enriched environment can result in a 7% to 10% increase in brain weight of young rats and a 20% increase in the number of connections in the visual cortex. Similar changes are seen in the brains of monkeys and cats raised in enriched environments. Even the brains of fruit flies housed in large communal cages with visual and odor cues show similar changes, compared with flies housed alone in small plastic vials (Technau, 1984).

Do similar effects occur in humans? Preschool children placed in "high-quality" day care (with lots of toys, educational experiences, and teacher interaction) often fare better in elementary school than children whose day care offers fewer opportunities for learning (Peisner-Feinberg, Burchinal, & Clifford, 2001). There isn't yet definitive evidence that human brains undergo enlargement similar to that of rats after environmental enrichment, because the current structural neuroimaging approaches used on children do not have the resolution necessary to detect change in individual neurons. However, suggestive data come from a study of London taxi drivers.

London is a sprawling city with hundreds of small, crooked streets. To receive an official license, London taxi drivers must study for up to three years and pass a grueling exam that requires them, for example, to indicate the shortest path between random London addresses. This means that licensed London taxi drivers are a group of people sharing an extensive fund of spatial knowledge.

Researcher Eleanor Maguire and her colleagues used MRI to compare brain volumes in a group of London taxi drivers with those of age-matched Londoners who had not studied the geography of their city so extensively (Maguire et al., 2000). The only part of the brain that differed significantly between the groups was the hippocampus: the taxi drivers had slightly larger hippocampal volumes than non–taxi drivers. Further, the size of the hippocampus differed even among individual taxi drivers: those who had been driving for more than a decade had a larger volume than those who had been driving for only a few years. One possible interpretation of these volume differences is that the intensive spatial learning in taxi drivers causes an increase in dendritic branching in hippocampal neurons—making those neurons take up more room, just like the rat neurons shown in Figure 2.7.

Interim Summary

- The brain and spinal cord make up the vertebrate central nervous system (CNS). The brain controls behavior through connections with the peripheral nervous system (PNS), which consists of sensory neurons coming from sensory receptors and motor neurons going to body muscles.
- The vertebrate brain is made up of several different regions that contribute to learning and memory, including the cerebral cortex, cerebellum, hippocampus, basal ganglia, and amygdala.
- Neurons, the building blocks of the nervous system, are capable of changing their function and modifying the way they process information.
- Modern structural brain-imaging techniques (including MRI and DTI) provide ways to measure variations in the brain structure of living humans without causing harm.
- Techniques for imaging neural structures in non-humans make it possible to collect detailed information about neural changes that occur during learning.
- Enriched environment studies show that learning experiences can have a profound impact on brain structure and on an individual's learning and memory abilities.

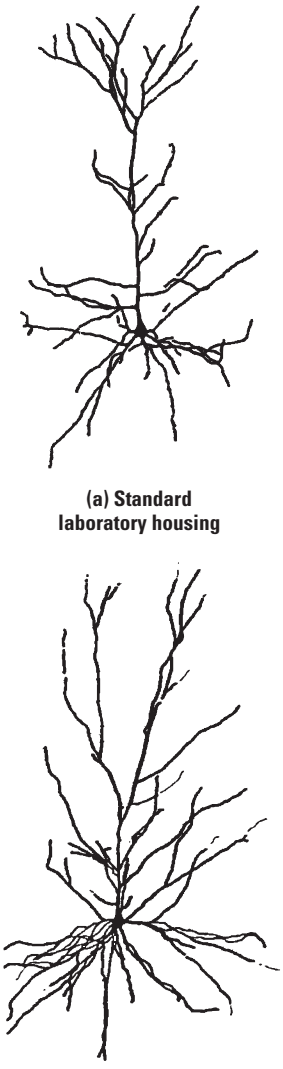


Figure 2.7 Deprived environment vs. enriched environment Representations of neurons from the cortex of (a) a rat raised in standard laboratory housing and (b) a rat raised in an enriched laboratory environment. Neurons from rats raised in enriched environments typically have more and longer dendrites than their experience-impoverished counterparts.

2.2 Functional Properties of Learning and Memory Systems

Modern brain scientists assume that brains are composed of multiple systems that specialize in collecting, processing, and storing particular kinds of information. But there is no one-to-one relationship, as phrenologists supposed, in which each individual function or ability is performed in a dedicated corner of the brain. Instead, one brain area may play a role in many functions, and one function may rely on contributions from many brain areas.

What determines how brain regions contribute to learning and memory processes? Two major factors are the kinds of *input* a region receives and the kinds of *output* it produces. These inputs and outputs are closely related to the stimuli and responses that behaviorists emphasized in their theories of learning (reviewed in Chapter 1).

What Brains Do

Chapter 1 defined learning as a process by which changes in behavior arise as a result of experience. Thus, when Pavlov's dogs began to salivate after hearing a sound that predicted food, this change in behavior—salivation in response to a sound—provided evidence that the dogs learned about the relationship between the sound and the food. But even before Pavlov began using the dogs in his experiments, they would salivate in response to food. Salivation during eating is a reflexive behavior that dogs (and other mammals) develop early in life; it helps the digestive system get ready to process incoming food.

reflex. An involuntary and automatic (unlearned) response.

A **reflex** is an involuntary and automatic response "hardwired" into an organism; in other words, it is present in all normal members of a given species and does not have to be learned. Just like Pavlov's dogs, humans salivate when eating food. This is only one of several reflexes that humans are biologically prepared to perform: newborns suck when they encounter a nipple (sucking reflex), hold their breath when submerged underwater (the diving reflex), and grasp a finger so tightly that they can support their own weight by hanging on to it (the palmar grasp reflex). Adults have reflexes, too, such as the knee-jerk reflex when the doctor hits your knee with a rubber mallet and an eyeblink reflex when someone blows air at your eye.

Why isn't this infant drowning?

Elli Thor Magnusson/Getty Images

Recall from Chapter 1 that Descartes explained reflexes as hydraulic movements caused by spirits flowing from the brain into the muscles. For many years, scientists accepted this explanation, assuming that there must be some kind of fluid carrying instructions from the brain to the muscles. It wasn't until the early twentieth century that researchers discovered, first, that there is no such fluid and, second, that the brain isn't in absolute control of the muscles at all.

Instead of a hydraulic fluid, there are two distinct types of nerve fibers (axons) connecting the muscles to the spinal cord: one set of fibers carrying sensory signals from the peripheral nervous system into the spinal cord, and a second set carrying motor signals back from the spinal cord to the muscles (Bell, 1811; Magendie, 1822). If a pinprick or other painful stimulus is applied to a dog's leg, its leg jerks reflexively (just as you'd pull your leg away if someone pricked you). If the sensory fibers are cut, the dog's sensation of pain disappears and the reflex fails to occur, although the dog can still move its leg normally. On the other hand, if the motor fibers are cut, the animal can still feel pain but, again, does not make reflexive leg movements. In the spinal cord, sensory fibers are separate from motor fibers. They run in two parallel nerve pathways, one devoted to sensing and the other to responding. This finding, called the *Bell–Magendie law of neural specialization*, represents the historical first step toward understanding the neural mechanisms of learning. Specifically, it shed light on how the nervous system responds to stimuli, and how it controls responses evoked by those stimuli.

Following up on the discovery of neural specialization, English physiologist Charles Sherrington (1857–1952) conducted many studies on dogs whose spinal cord had been surgically disconnected from their brain, so that the spinal cord no longer received any brain signals. Such surgically altered dogs show many basic reflexes, such as jerking their leg away from a painful stimulus. Because the brain cannot contribute to these reflexes, they must be generated by the spinal cord alone. In fact, we now know that sensory inputs can activate motor fibers traveling out of the spinal cord, without waiting for signals from the brain. (The sensory pathways in the spinal cord are largely separate from the motor pathways there, yet at the same time, sensory and motor neurons are closely interconnected, throughout the nervous system.) If you've ever stuck your hand into dangerously hot or cold water and jerked it away almost before realizing what you've done, or watched your knee jerk in response to the doctor's rubber mallet, then you've experienced your spinal cord responding without receiving any help from your brain.

Sherrington concluded that such simple "spinal reflexes" could be combined into complex sequences of movements and that these reflexes were the building blocks of all behavior (Sherrington, 1906). Sherrington's description of reflexes differed from that of Descartes in assuming that spinal reflexes did not depend on the brain and did not involve the pumping of spirits or fluids into the muscles. Sherrington received a Nobel Prize in 1932 for his work in this area, and he is now considered to be one of the founding fathers of neuroscience. His ideas provided the groundwork and motivation for Pavlov's early investigations of reflex conditioning in dogs (Pavlov, 1927) and have continued to influence learning and memory researchers ever since.

If the spinal cord controls reflexes and if complex actions can be described as combinations of these reflexes, then where does the brain come in? Sensory fibers enter the spinal cord and connect to motor fibers there, but some fibers also travel up to the brain. The brain processes these inputs and produces its own outputs, some of which may travel back down the spinal cord and out to the muscles. The parallel sensory and motor pathways traveling up and down the spinal cord, to and from the brain, are similar to the parallel sensory and motor pathways that were identified traveling into and out of the spinal cord.

Incoming Stimuli: Sensory Pathways into the Brain

Let's focus first on the sensory pathways that provide inputs to the brain. As noted earlier in this chapter, most sensory inputs enter the brain through the thalamus. The thalamus in turn distributes these inputs to cortical regions specialized for processing particular sensory stimuli, such as the primary auditory cortex (A1), for sound; the primary somatosensory cortex (S1), for sensations from skin and internal organs; and the primary visual cortex (V1), for sight. A1 is located in the temporal lobe, S1 in the parietal lobe, and V1 in the occipital lobe (Figure 2.8). Such areas are collectively called *primary sensory cortices*, as they are the first stage of cortical processing for each type of sensory information. Each primary sensory cortex can then transmit outputs to surrounding cortical regions for further processing. For example, the primary visual cortex may start the processing of stimuli from the eye by extracting simple features—say, lines and shading—from a visual scene; later stages of cortical processing

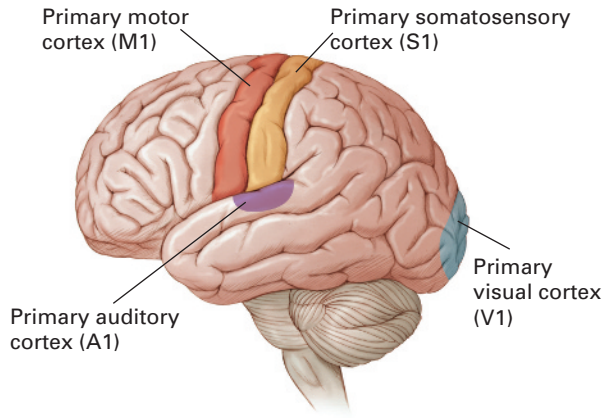


Figure 2.8 Cortical regions for processing inputs and outputs Specific regions of cerebral cortex are specialized for processing light (primary visual cortex), sound (primary auditory cortex), and sensation produced by physical movement (primary somatosensory cortex). Other regions are specialized for generating coordinated movements (primary motor cortex).

elaborate by detecting motion or shape in the scene and, finally, by responding to features of individual objects and their meaning. Damage to primary sensory cortices can eliminate particular perceptual abilities. For instance, people with damage to V1 can become blind, even though their eyes are in perfect working order, and damage to A1 can cause deafness.

Outgoing Responses: Motor Control

Just as various brain regions are specialized for processing sensory inputs, other brain regions are specialized for processing the outputs that control movements. Chief of these is the primary motor cortex (M1), which generates coordinated movements. M1 is located in the frontal lobe, adjacent to S1 in the parietal lobe (Figure 2.8), and it sends output to the brainstem, which in turn sends instructions down the spinal cord to activate motor fibers that control the muscles.

M1 gets much of its input from the frontal lobes, which are responsible for making high-level plans based on the present situation, past experience, and future goals. (Should you pick up that hot coffee cup? Should you try to catch that ball with one hand or two?) Other important inputs come from the basal ganglia and cerebellum, which help to translate the high-level plans into concrete sets of movements. All these inputs help determine the outputs that M1 sends to the brainstem. Other motor areas—including the cerebellum, basal ganglia, frontal cortex, and the brainstem itself—also produce their own outputs, all of which converge on the spinal cord and travel from there to the muscles. Complex motor movements—such as picking up a hot coffee cup without spilling the liquid or burning your hand, or picking up an egg without crushing it, or dancing without stepping on your partner's toes—require exquisitely choreographed interactions between all of these brain structures and the muscles they control.

Let's consider one of these examples in greater detail: you see a cup of coffee and pick it up (Figure 2.9). The process begins with visual input from your eyes traveling to your visual cortex (V1), which helps you find and identify the cup. Regions in your frontal lobes coordinate the necessary plans for grasping the cup, which your motor cortex (M1) then directs by means of outputs through the brainstem, down sets of fibers in the spinal cord, and out to the muscles of the arm and fingers. As you reach for the cup, your basal ganglia and cerebellum continually track the movement, making tiny adjustments as necessary. These brain regions enable you to exert just the right amount of pressure on the cup: enough to lift it against gravity, but not so much that you yank it off the table and spill the contents. As you pick up the cup, sensory information from touch, heat, and pressure receptors in your fingers travels back up your arms, through sensory fibers in the spinal cord, and to the somatosensory cortex (S1), providing evidence that the cup is firmly in your hand. If the handle of the cup is hotter than expected, it could produce a reflexive withdrawal of the hand. This response is the kind of spinal reflex studied by Charles Sherrington; the short path from the hand to the spinal cord and back is sometimes called a *reflex arc*.

All that input and output just to pick up a cup—before you've even taken your first sip! Infants of many vertebrate species, including humans, are born fairly clumsy and spend a large part of their infancy and childhood learning how to walk or fly or swim gracefully, reach accurately, move throat and tongue muscles to produce coherent sounds, and so on. This relatively long period spent learning coordinated motor control reflects both the complexity of the operations and the many brain structures that have to interact with one another and with the outside world to perform them.

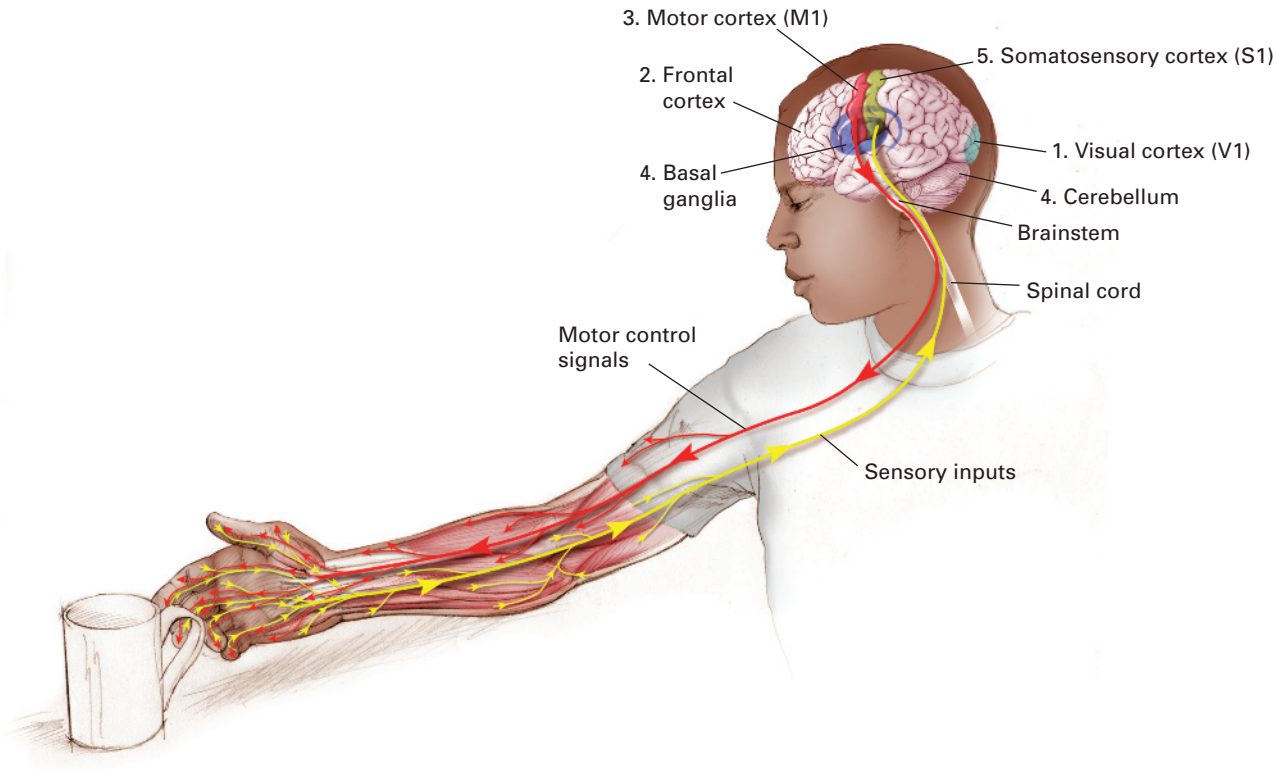


Figure 2.9 How to pick up a cup of coffee (1) Visual input from V1 helps you locate the coffee cup and its handle. (2) The frontal cortex helps you plan the movement. (3) Outputs from the motor cortex (M1) travel through the brainstem and down sets of fibers in the spinal cord to the muscles in the arm, causing you to reach out your hand. (4) The basal ganglia and cerebellum continuously monitor whether your hand is on track, making tiny adjustments to ensure that your hand reaches the correct target. (5) Sensory signals travel back up the arm and spinal cord, through a second set of fibers, to somatosensory cortex (S1), confirming that the cup has been grasped.

The Synapse: Where Neurons Connect

So far, we've been describing the transmission of signals into and out of the brain as if these signals flowed from one place to another in the nervous system like water through a pipe (similar to the way Descartes described the mechanisms of behavior). What really happens is that neurons throughout the nervous system are continually communicating with one another in vast networks that are similar in some ways to social networking systems such as Twitter or Facebook. It is this communication between neurons that makes learning and memory possible.

Generally, neurons that communicate with each other are not actually physically connected. Rather, communicating neurons are separated by a narrow gap of about 20 nanometers (1 nanometer is one-billionth of a meter), called a **synapse**, across which the neurons pass chemicals (Figure 2.10a). Most synapses are formed between the axon of the **presynaptic**, or sending, neuron and a dendrite of the **postsynaptic**, or receiving, neuron, but synapses can also be formed between an axon and a cell body, between an axon and another axon, and even between dendrites.

Neurons contain **neurotransmitters**, chemical substances that can cross a synapse to affect the activity of a postsynaptic neuron. Neurotransmitters are kept conveniently on hand at the end of the presynaptic axon, in packets known as *vesicles*. To transmit a signal, one or more vesicles of the presynaptic

synapse. A narrow gap between two neurons across which chemical messages can be transmitted.

presynaptic. On the sending side of a synapse.

postsynaptic. On the receiving side of a synapse.

neurotransmitter. One of several classes of molecule released by neurons to carry chemical messages to other neurons.

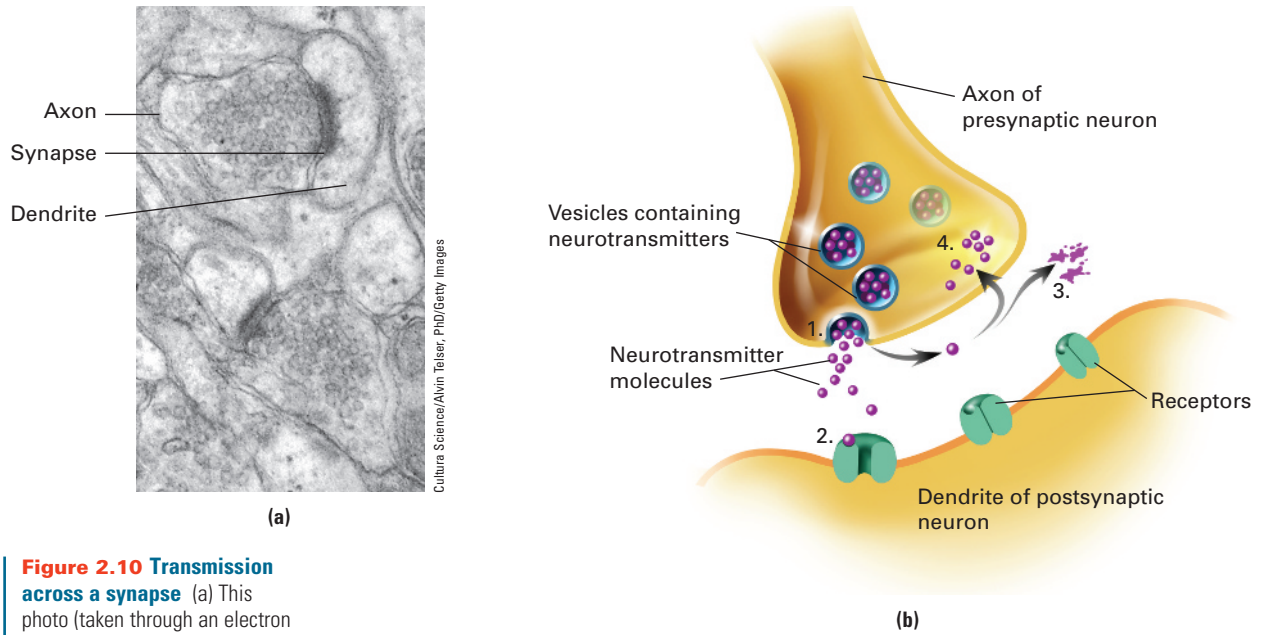


Figure 2.10 Transmission across a synapse (a) This photo (taken through an electron microscope) shows the tiny gaps, or synapses, between neurons. Vesicles filled with neurotransmitters, ready for release into the synapse, are visible as circular packets inside the presynaptic neuron. (b) A signal is transmitted between neurons when (1) the presynaptic neuron releases neurotransmitter into the synapse and (2) the neurotransmitter molecules dock at receptors on the surface of the postsynaptic neuron. This may activate the receiving neuron. Leftover neurotransmitter in the synapse is either (3) broken down or (4) reabsorbed into the presynaptic neuron.

receptor. A specialized molecule, located on the surface of a neuron, to which one or more particular neurotransmitters can bind; when a neurotransmitter activates a receptor, effects may be initiated in the neuron.

axon release neurotransmitters into the synapse (Figure 2.10b). Several different chemicals act as neurotransmitters. Major ones include *glutamate*, *gamma-aminobutyric acid* (*GABA*), *acetylcholine*, *dopamine*, *norepinephrine*, *epinephrine*, *and serotonin*. Once neurotransmitters have been released into the synapse, the next step is for the postsynaptic neuron to collect them. **Receptors** are molecules embedded in the surface of the postsynaptic neuron that are specialized to bind with and respond to particular kinds of neurotransmitters.

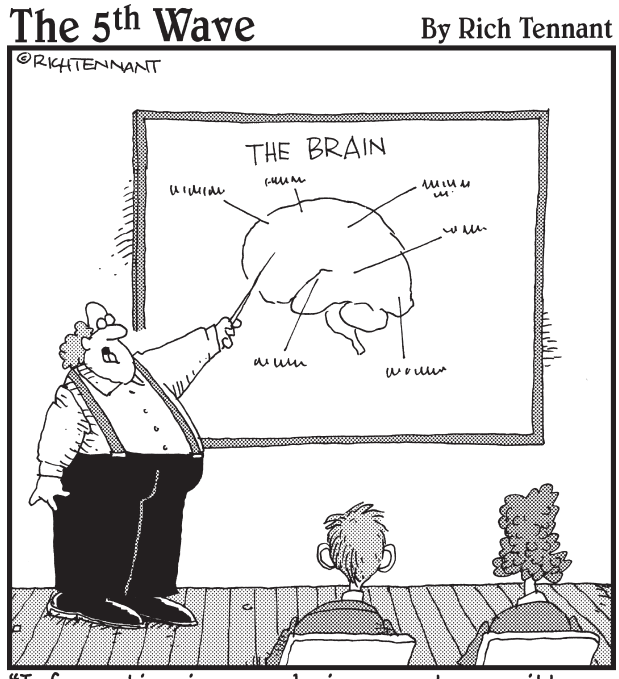
The effect of a particular neurotransmitter depends on what its corresponding postsynaptic receptors do when activated. Some receptors open a channel for the flow of electrically charged molecules into or out of the cell, thus changing the charge characteristics in a small area of the neuron. Similar electrical changes may be occurring simultaneously in other locations on the neuron as other receptors on other dendrites become active. The neuron's cell body integrates this cocktail of electrical signals; if the total electrical charge exceeds a threshold, the neuron "fires," propagating an electrical charge, called an *action potential*, down its axon. This propagation is an all-or-nothing event: either the neuron fires or it doesn't; there is no in-between stage. When a neuron fires, sending an electrical charge to the end of the axon, it causes the release of neurotransmitters there.

Some neurotransmitters—glutamate, for example—are *excitatory*, activating receptors that tend to increase the likelihood of the postsynaptic neuron firing. Other neurotransmitters—such as GABA—are *inhibitory*, activating receptors that tend to decrease the likelihood of the postsynaptic neuron firing. Usually, a given neuron produces and releases only one kind of neurotransmitter. But that neuron may be able to respond to signals from many different presynaptic neurons, each releasing a different kind of neurotransmitter.

After a neuron fires, there is a brief period, called a *refractory period*, during which it can't fire again, no matter how much input it receives. Once this refractory period has passed, the neuron is again open for business. If the neuron is still receiving a lot of input from its neighbors, it may fire again and again in rapid succession, interrupted only by the refractory period after each action potential. If the excitatory inputs are less frequent or less strong or if there is a lot of inhibitory input, some time may pass before the neuron fires again.

In the meantime, neurotransmitters have to be cleared out of the synapse so that the synapse can receive future signals. In some cases, this consists of breaking the neurotransmitter molecules down into their constituent parts in a process called *inactivation*. In other cases, they are brought back into the presynaptic neuron and recycled for future use, a process called *reuptake*. When cleanup is complete, the synapse and receptors are ready to receive new transmissions.

Several areas in the brainstem contain neurons that send axons widely throughout the brain; when these neurons fire, they release neurotransmitters called **neuromodulators** that can affect activity in entire brain regions, rather than just at a single synapse. Neuromodulators alter, or modulate, how neurons transmit and receive signals, although they themselves are not part of the signal. For example, acetylcholine often functions as a neuromodulator, and one of its effects is to temporarily alter the number of receptors that have to be active before a postsynaptic neuron can fire. If you think of synaptic transmission as a message, then acetylcholine levels help determine whether the message is heard as a whisper or a shout. Many human diseases that affect learning and memory seem to involve a global decline in neuromodulators. Examples include Alzheimer's disease, which is associated with a reduction in acetylcholine (Francis, Palmer, Snape, & Wilcock, 1999), and Parkinson's disease, which is characterized by a reduction in dopamine (Evans & Lees, 2004).



neuromodulator. A neurotransmitter that acts to modulate activity in a large number of neurons rather than in a single synapse.

Test Your Knowledge

Synaptic Transmission

Several complex processes that occur at the synapse allow neurons to communicate. Which, if any, of the statements below do not describe one of these processes? (Answers appear in the back of the book.)

1. Neurotransmitters are reabsorbed by the axon that released them.
2. Neurotransmitters are broken down while they remain in the synapse.
3. Neurotransmitters bind to the dendrite of the postsynaptic neuron.
4. Neurotransmitters are released from vesicles and enter the synapse.

Observing Learning-Related Changes in Brain Function

Given that learning is a process that can lead to changes in behavior, and that brains control behavior through changes in neural activity, it is clear that learning must be associated with new patterns of activity in the brain. However, knowing that your brain is doing something different after years of practicing

or after experiencing a traumatic event is a far cry from knowing what it is doing differently or why. Even if structural imaging techniques reveal that experience has led to physical changes in parts of neurons or to increases in the volume of a brain region, understanding how these changes contribute to performance is not straightforward. Neuroscientists are attempting to gain a clearer understanding of how experiences change brain function by monitoring specific changes in activity that occur within the central nervous system before, during, and after such experiences.

Functional Neuroimaging and Electroencephalography

functional neuroimaging. Techniques (such as fMRI or PET) for observing the activity or function of a living brain.

As noted above, structural neuroimaging methods (such as MRI) allow researchers to look at the *structure* of a living human brain, whereas **functional neuroimaging** allows them to look at the *activity*, or function, of a living brain. For example, when a brain structure becomes active, it requires more oxygen. Within 4 to 6 seconds, blood flow (with its cargo of oxygen) increases to that region. On the other hand, when a brain structure becomes less active, it requires less oxygen, and blood flow decreases. By tracking local changes in blood flow, researchers can discover which brain regions are active or inactive.

Rather than focusing on where blood flow is heavier in the brain, functional neuroimaging studies typically examine how blood flow in a particular brain region *changes* depending on what the person is doing or thinking. To see such changes in blood flow, researchers may first scan the brain while the person is relaxed—not doing anything. The resulting image is called a *baseline* image. Even though the person isn't performing any task, the brain is still active. Next, the researchers scan the brain again while the person is performing a task, such as looking at pictures or reading a story. (The pictures or words are projected on the inside ceiling of the scanner so that the person can see them while lying on his or her back.) During the task, some areas of the brain should become more active than they were at baseline. Others might decrease in activity. From each point (or pixel) in the image, researchers then subtract the activity at that identical point in the baseline image. The result, called a **difference image**, shows how activity at each point in the image has increased or decreased in the task condition compared with the baseline condition (Figure 2.11a).

difference image. An image of differences in brain activity obtained by taking an fMRI or PET image of a person performing a particular task, then subtracting the image of the same individual at baseline (not performing a task).

Usually, the difference image is color coded, with white, red, or yellow indicating areas where blood flow *increased* most during the task relative to the baseline. Colors such as blue and green may indicate where blood flow *decreased* most during the task. Uncolored areas indicate regions where no significant change took place. For example, the difference image in Figure 2.11a shows the parts of the brain that become significantly more active when a person is viewing pictures, confirming the current understanding that areas of the cerebral cortex in the occipital lobe are important for visual processing. When used in studies of learning and memory, functional neuroimaging methods can reveal differences in brain activity that are associated with performing different kinds of memory tasks (for instance recognizing faces versus recalling what happened at a recent party), differences associated with successful recall versus forgotten facts, and differences in memory function associated with particular disorders (for example, by comparing activity in people with and without schizophrenia as they perform a memory task).

Typically, researchers do not rely on measurements from a single person to decide which brain regions are most likely to show changes in activity levels during performance of a particular task. Instead, they usually collect data from multiple individuals and then calculate a mean difference image for a group (Figure 2.11b). One consequence of this approach is that the results of functional neuroimaging studies emphasize differences in activity that are prevalent

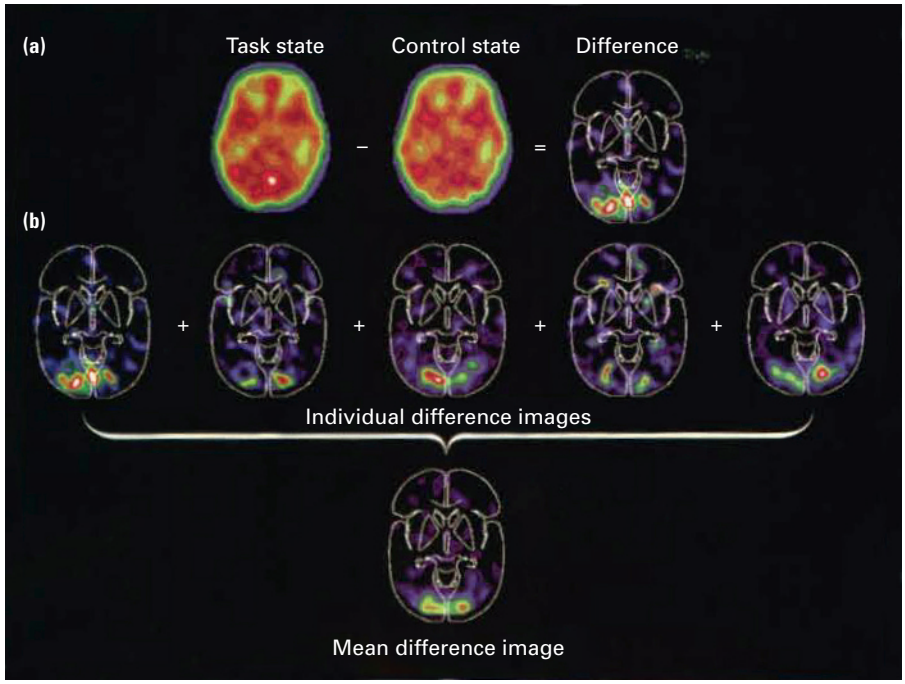


Figure 2.11 Creating a difference image with functional neuroimaging (a) A PET scan detecting blood flow as the brain performs a certain task (in this case, viewing pictures projected on the inside of the scanner). A baseline image taken while the participant is not performing the task is subtracted from an image collected during performance of a task to create a difference image, color coded to show areas where blood flow significantly increased (or decreased) in the task condition compared with the baseline condition. The white lines are a standard drawing of the same cross section as the PET images to clarify which brain regions correspond to the colored areas. (b) Difference images from multiple individuals are combined to calculate an average difference image.

across many participants, but do not necessarily reveal the full suite of changes in activity that occur within any particular individual.

Two commonly used functional neuroimaging technologies are **positron emission tomography (PET)** and **functional magnetic resonance imaging (fMRI)**. PET measures brain activity by detecting radiation from the emission of subatomic particles called positrons, associated with the brain's use of glucose from the blood. fMRI makes use of the same MRI technologies employed for structural imaging described above. Researchers can take an MRI at baseline and a second one while the person is performing a task. Oxygenated blood produces slightly different signals than deoxygenated blood, so there are fluctuations in the signal received from areas of the brain that undergo a change in activity level during the task.

positron emission tomography (PET). A method of functional neuroimaging based on detecting radiation from the emission of subatomic particles called positrons, associated with the brain's use of glucose from the blood.

functional magnetic resonance imaging (fMRI). A method of functional neuroimaging based on comparing an MRI of the brain during performance of a task with an MRI of the brain at rest.

Although PET and fMRI are powerful tools for observing the brain in action, they are only indirect measures of brain activity; respectively, they measure glucose utilization and blood oxygenation in a brain region rather than directly measuring the activity of neurons. Also, because functional neuroimaging studies typically focus on differences in activity under different conditions (through difference images), they tend to emphasize associations between specific brain regions and particular functions (much like phrenology), as opposed to revealing the full range of brain activity that contributes to mental and physical functioning. Finally, current functional neuroimaging techniques are comparatively slow: fMRI allows images to be taken every few seconds, while PET images can be taken only every few minutes, but changes in the brain occur much more rapidly than that. To track changes in real time, other techniques, such as electroencephalography, are needed.

Electroencephalography (EEG) is a technique for measuring electrical activity in the brain, using the same type of recording electrodes that are used in electrocardiograms. (The Greek word *enkephalos* means "brain," and so "electro-encephalo-graphy" means drawing or graphing the electrical activity

electroencephalography (EEG). A method for measuring electrical activity in the brain by means of electrodes placed on the scalp; the resulting image is an electroencephalogram (also EEG).

of the brain.) The electrodes simply record changes in electrical activity. When such electrodes are placed on a person's chest, they measure electrical activity resulting from heart contractions. When the electrodes are placed on the scalp, they measure the combined tiny electrical charges of large numbers of neurons in the brain, especially those near the location on the skull where the electrodes are placed. The resulting picture is called an *electroencephalogram* (also abbreviated as EEG).

Just as blood is always flowing through the brain, so electrical activity is always occurring in the brain, reflecting the firing patterns of neurons. The exact pattern of activation changes depending on what the brain is doing. For example, when a tone sounds, sensory receptors in the ear become active, and signals travel to the primary auditory cortex (A1), affecting electrical activity there. But detecting this particular electrical change in an EEG is difficult because lots of other neurons in other brain areas that are not involved in hearing may also be active—those responding to whatever visual stimuli happen to be in front of you, for instance, or those activated as you wiggle your fingers and think about what you want to have for lunch.

To detect an electrical change associated with hearing a stimulus, such as a tone, researchers typically present the same stimulus hundreds of times and then average the EEGs produced throughout those repetitions in a given individual. The principle is that activity in other brain areas will come and go, but only the neurons responding to the specific sensory stimulus will be consistently activated each time the stimulus is repeated—and so only their activity patterns will survive the averaging process. EEGs averaged across many repetitions of the same event are called **event-related potentials (ERPs)**. Just as functional neuroimaging shows how the brain changes while performing a task, so ERPs can be used to show different brain states at different stages of learning, such as how a person's brain responds to different sounds as the person gradually learns to make subtle distinctions between them (discussed in Chapters 3 and 6).

event-related potential (ERP). Electroencephalograms (EEGs) from a single individual averaged over multiple repetitions of an event (such as a repeated stimulus presentation).

Compared with fMRI and PET, EEG recording is a simple and cheap way to monitor changes in brain activity during learning and memory tasks. In addition, EEG can detect rapid changes in the brain with more precision than fMRI or PET. Yet what EEG gains in temporal precision it often sacrifices in spatial precision. Whereas fMRI and PET can localize activation to within a few millimeters, EEG signals show activity over a wide swath of the brain. Some memory researchers are combining functional neuroimaging and EEG methods to generate images that show precisely when and where neural activity occurs during memory storage and recall by humans.

To record neural activity from humans as they perform tasks, researchers attach multiple electrodes to a person's scalp. Traditionally, signals from electrodes are collected from wires attached to the electrodes (as shown here for the infant), but recent wireless technologies make it possible to record neural activity in any setting. How might EEG be used to measure functional brain changes that have occurred in the adult model as a result of her modeling experiences?

Aaron MCcoy/Getty Images

www.emotiv.com

Recording from Neurons

In the brain, memory functions are affected not only by *which* neurons fire but also by *how often* they fire. Neuroimaging and EEG studies can reveal the contributions of large areas of the brain to learning and memory, but they don't reveal much about which individual neurons are firing or how often. To gather this information, researchers have to record neural activity directly. **Neurophysiology** is the study of the activity and function of neurons.

neurophysiology. The study of the activity and function of neurons.

One technique scientists use to measure the firing patterns of individual neurons is **single-cell recording** (the single cell in this case is a neuron). The microelectrodes that are used in this method function somewhat like EEG electrodes, but they are shaped like extremely thin needles and can penetrate brain tissue with a minimum of damage. A microelectrode can be inserted in brain tissue until its tip is very close to, or sometimes even inside, a target neuron. In some cases, researchers anesthetize an animal and surgically implant one or more microelectrodes in the brain areas they wish to study. Then, when the animal wakes, the researchers can record from the neuron(s) as the animal goes about its daily business. (Most animals don't seem to be much bothered by, or even aware of, the wires connected to their heads.) Such experiments allow researchers to determine what role a given neuron or network of neurons might play in the animal's behavior. Alternatively, if the researcher is interested in looking more closely at how individual neurons interact, it is possible to remove pieces (or "slices") of a brain, keep the neurons alive in a bath of nutrients, and record their activity in the slices.

single-cell recording. Use of an implanted electrode to detect electrical activity (spiking) in a single cell (such as a neuron).

Single-cell recordings have provided some of the most dramatic evidence to date of how neural firing relates to behavior. For example, Apostolos Georgopoulos and colleagues recorded spike patterns from the motor cortex of a monkey while the monkey moved a joystick in different directions (Figure 2.12a; Georgopoulos, Taira, & Lukashin, 1993). Some neurons fired most strongly when the monkey pushed the lever in a particular direction. Figure 2.12b shows recordings from one such neuron as the monkey moved the lever toward different compass points. Each vertical line in the recording represents one action potential, sometimes referred to as a *spike*. When the monkey moved its arm toward the point labeled 6 in Figure 2.12a, the neuron initially produced several spikes, then fell silent. When the monkey moved its

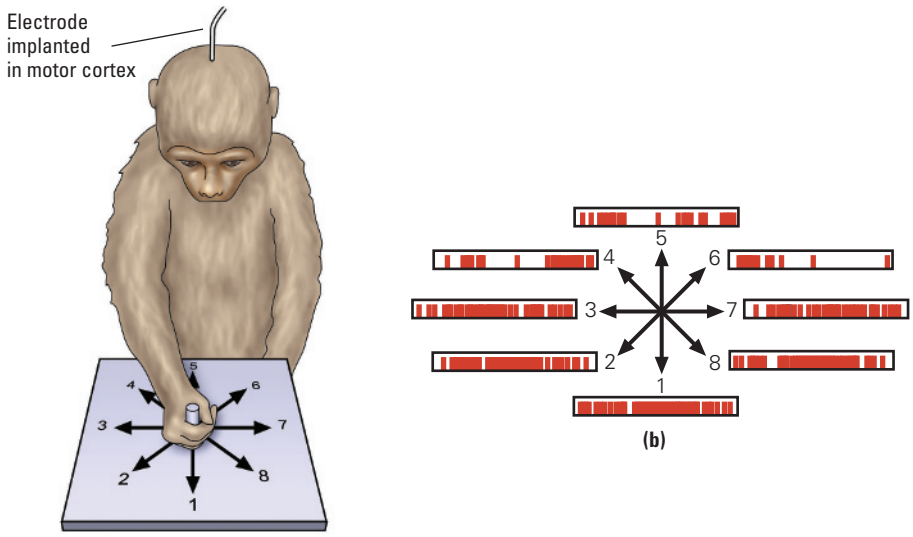


Figure 2.12 Recording from single neurons (a) Researchers implanted recording electrodes into the motor cortex of a monkey, which was then trained to move a joystick in different directions. (b) One recorded neuron showed spiking behavior (illustrated as vertical lines) when the monkey moved its arm. This neuron fired most when the monkey moved its arm toward position 1 and least when it moved its arm toward position 5. Thus, this neuron is tuned to fire during movements away from the monkey's body.

(b) Information from Georgopoulos et al., 1993.

arm to a slightly different position, point 7, the neuron produced a more sustained burst of activity, continuing to spike for the duration of the movement. But when the monkey moved its arm directly away from its body, toward point 1, the neuron really went into action, spiking as fast and frequently as it could. By contrast, when the monkey moved its arm in the opposite direction, toward its body (point 5), the neuron was much less active. Thus, this neuron's firing patterns are correlated with arm movements, and neuroscientists would say it is specialized, or "tuned," to fire maximally during movements in a particular direction: away from the body. Georgopoulos and colleagues found that other neurons in the motor cortex were tuned to fire during arm movements in other directions. Given what we know about the motor cortex from functional imaging studies, it is reasonable to assume that these neurons may be playing a direct role in issuing the commands that cause the monkey's arm to move. Because monkeys generally must be trained to move a joystick in different directions in laboratory experiments, such recordings can potentially reveal how the firing patterns of neurons change as monkeys learn to perform such tasks. In fact, such research has led to new technologies that enable both monkeys and humans to learn to control the movements of robotic arms simply by thinking about where they want the arm to move (discussed in Chapter 8).

Interim Summary

- Reflexes are natural, automatic responses to stimuli. Sherrington and other early neuroscientists believed that all complex learning involved combining simple spinal reflexes.
- In the brain, sensory signals (produced by stimuli) are initially processed in cortical regions specialized for processing such signals, and ultimately lead to activity in other cortical regions, such as the motor cortex, that are specialized for coordinating movements (responses).
- The neural transmission that enables stimuli to generate responses takes place across tiny gaps, or synapses: the presynaptic, or sending, neuron releases neurotransmitters into the synapse; these chemicals cross the synapse to activate receptors on the postsynaptic, or receiving, neuron.
- Functional neuroimaging methods (such as fMRI and PET) allow researchers to track brain activity during the performance of memory tasks by measuring increases and decreases in glucose utilization and blood oxygenation in different brain regions.
- Electroencephalographic recordings make it possible to track the activity of large populations of neurons over time, as well as monitor how such activity changes as learning progresses.
- Single-cell recordings allow researchers to directly monitor and record the electrical activity (or "firing") of single neurons and changes in their firing patterns that occur during learning or the recall of memories.

2.3 Manipulating Nervous System Activity

Imagine that a Martian scientist comes to Earth and encounters an automobile, a method of transportation unknown on Mars, powered by an energy source also unknown to Martians. Since the Martian speaks no Earth languages and can't simply ask a mechanic for an explanation, how might she learn how the

car works? One way would be to look under the hood and examine the many components there. But studying the car's "structure" would only get her so far; to learn about the car's function, she'd have to take it for a test drive and see how it behaves normally. However, simply seeing cars in action cannot reveal what makes them go.

One approach the Martian might use to better understand cars would be to investigate what the different parts do. For instance, she could try disconnecting or removing parts, one at a time, noting the consequences in each case. If she removed the axle, she'd learn that the motor would work but couldn't transfer energy to make the wheels turn. If she removed the radiator, she'd learn that the car would run but would quickly overheat. In the end, by discovering the function of each of the car parts, the Martian could probably develop a pretty good idea of how the car works.

Taking a Hand in Brain Function

Neuroscientists trying to understand how nervous systems make it possible for organisms to learn and remember face a challenge similar to the Martian's. No surprise then that one of the earliest approaches researchers took was something like the Martian's: to examine people with one or more pieces of their brains damaged or missing to see how such losses affect performance. Although no scientist would disassemble the brain of a living human the way the Martian might disassemble a car, humans regularly suffer damage to one or more brain areas, through accident, injury, or disease, making it possible to explore the effects of missing or damaged brain regions on learning and memory abilities. Neuroscientists also have developed techniques for controlling or changing the firing patterns of neurons by triggering their electrical activity or by introducing foreign chemicals into the brain. How each of these different approaches to intervening in brain function can be used to better understand the neural substrates of learning and memory is described in the following pages.

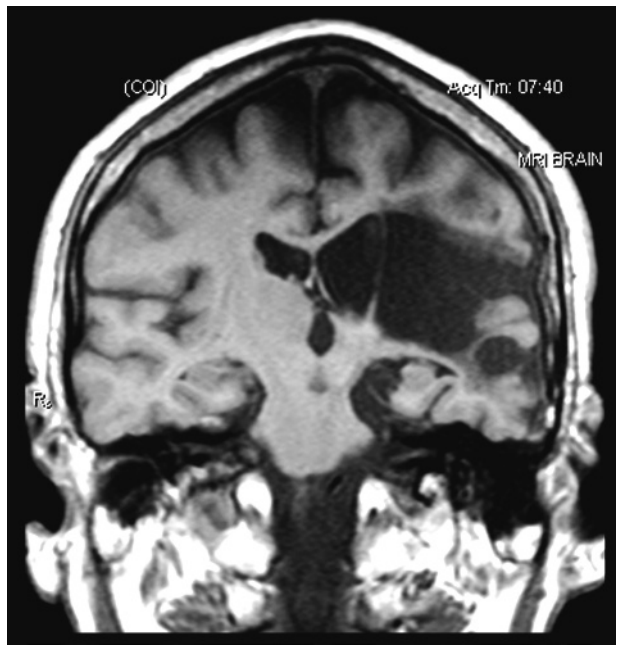
neuropsychology. The branch of psychology that deals with the relation between brain function and behavior.

Effects of Brain Injuries

Neuropsychology is the branch of psychology that deals with the relation between brain function and behavior, usually by examining the functioning of patients with specific types of brain damage. These individuals volunteer their time and effort in experiments that test their learning and memory abilities, as well as other kinds of cognitive function—language, attention, intelligence, and so on. The test results can potentially be used to guide a patient's rehabilitation, but they also serve a research purpose. By recognizing patterns in the impaired and spared abilities of a group of patients who have experienced damage to a similar region of the brain, researchers hope to build a better picture of that brain region's normal function—just like the Martian trying to understand what a radiator does by watching what happens to a car that doesn't have one.

Animal researchers have conducted parallel studies by removing or deactivating specific brain regions to create animal "models" of humans with brain damage. Because human brain damage is almost always caused by accident, injury, or illness, every

Brain injuries can lead to the loss of large portions of brain tissue. In this MRI image, missing cerebral cortex appears as a dark region on the right side of the image. Is this lesion more likely to be in the temporal lobe or the occipital lobe?



Living Art Enterprises/Science Source

patient's damage—and disability—is slightly different. By contrast, in animal models, researchers can remove or disable specific brain regions with great precision, making it much easier to compare results across individuals. Instances in which the experimental results from human patients and animal models converge give the clearest picture of how the brain works normally and how it functions after damage.

engram. A physical change in the brain that forms the basis of a memory.

Some of the most famous experimental brain lesion studies of learning and memory were conducted by Karl Lashley (1890–1958), an American psychologist who was looking for the location of the **engram**—the supposed physical change in the brain that forms the basis of a memory (also referred to as a *memory trace*). Lashley would train a group of rats to navigate a maze, and then he'd systematically remove a different small area (covering, say, 10%) of the cortex in each rat. He reasoned that once he'd found the lesion that erased the animal's memories of how to run through the maze, he would have located the site of the engram (Lashley, 1929).

Alas, the results were not quite so straightforward. No matter what small part of the cortex Lashley lesioned, the rats kept performing the task. Bigger lesions would cause increasingly large disruptions in performance, but no one cortical area seemed to be more important than any other. Hence, Lashley couldn't find the engrams for memories formed during maze learning. Finally, in mock despair, he confessed that he might be forced to conclude that learning "simply is not possible" (Lashley, 1929).

theory of equipotentiality. The theory that memories are stored globally, by the brain as a whole, rather than in one particular brain area.

Eventually, Lashley settled on a different explanation. He endorsed the **theory of equipotentiality**, which states that memories are not stored in one area of the brain; rather, the brain operates as a whole to store memories. Although Lashley is often credited with formulating this theory, it was actually first proposed in the 1800s as an alternative to phrenology (Flourens, 1824). In the theory of equipotentiality, memories are spread over many cortical areas; damage to one or two of these areas won't completely destroy the memory, and over time the surviving cortical areas may be able to compensate for what's been lost.

Lashley's work, and his endorsement of the theory of equipotentiality, were milestones in the neuroscience of memory because researchers could no longer take for granted the compartmentalized structure–function mapping that phrenologists had proposed. But, like the phrenologists before him, Lashley was only partly right. The phrenologists were in fact on the right track when they proposed that different brain areas have different specialties; the specialization just wasn't as extreme as they thought. Lashley was also on the right track when he proposed that engrams aren't localized to specific areas of the cortex, but we now know that the cortex isn't quite as undifferentiated as he came to believe. The truth is somewhere in the middle. Moreover, as you will discover in subsequent chapters, part of the reason Lashley's experiments did not work out the way he expected was because of his assumption that memories formed during maze learning were stored only in cerebral cortex. If Lashley had instead made his lesions beneath the cortex, he might have discovered that other brain regions (such as the hippocampus) more strongly affect spatial learning and memory (the role of the hippocampus in spatial learning is discussed in Chapters 3 and 7).

Useful as brain lesion experiments are, they are limited in what they can reveal. Suppose a researcher lesions part of a rat's cortex and then finds, as Lashley did, that the rat can still learn how to get around in a maze. Would that prove that the lesioned cortical area is not involved in spatial memory? Not necessarily; the rat may now be learning the maze in a different way. This would be analogous to your being able to find your way around a house with the lights out, even though you use visual input when it's available. Data from lesion

studies are strongest when supplemented by data from other techniques showing that a brain region normally participates in a given behavior, or that artificial stimulation of that region affects performance in related tasks.

Test Your Knowledge

Equipotentiality versus Phrenology

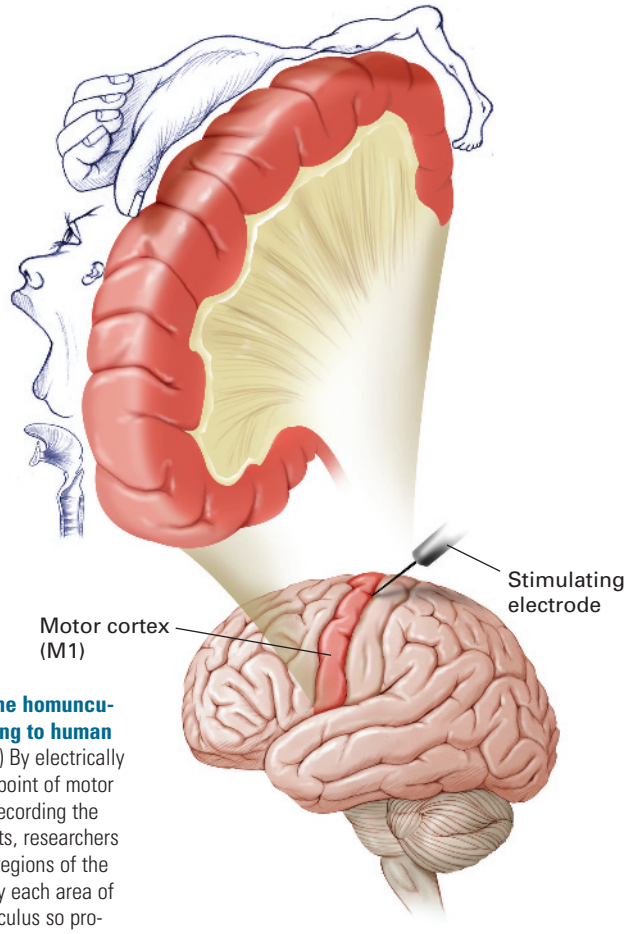
What are the main differences between the explanations of brain function proposed by Franz Joseph Gall and those ultimately proposed by Karl Lashley? What evidence did each use to support his viewpoint? (Answers appear in the back of the book.)

Electromagnetic Control of Neurons

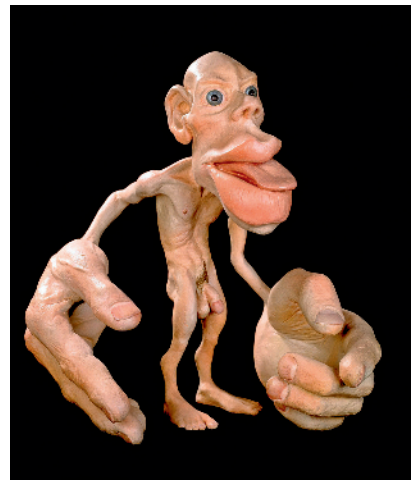
In addition to using microelectrodes to observe neural activity, researchers can also use electrodes to stimulate neural activity by delivering tiny amounts of electrical current into the brain. As you read above, when neurons fire, an action potential sweeps down the axon, triggering the release of neurotransmitters into the synapse. A stimulating electrode can cause spiking activity to happen where and when the researcher is ready to observe and record it.

Electrical stimulation of neurons was used as early as the 1800s, to prove that neural activity in the motor cortex produces motor behavior. Pavlov, for instance, was able to produce a wide range of movement patterns in an anesthetized dog by electrically stimulating its motor cortex (Pavlov, 1927). Similar techniques can be used in primates to map which parts of the motor cortex are responsible for generating movements in particular body parts. For example, electrical stimulation delivered to certain neurons in M1 in the right hemisphere, near the top of the brain, cause a monkey's lips to twitch. A little farther down and an arm might twitch. Still lower and movements occur in the legs. By painstakingly testing the effects of stimulating each point in M1, scientists can draw a map—called a *homunculus* (or "little man")—on the surface of M1, showing which parts of the body each subsection of M1 controls. The homunculus for M1 in humans (Figure 2.13a) has been worked out with the assistance of patients who were candidates for brain surgery (for example, to remove a tumor). Before removing any brain tissue, neurosurgeons do preliminary testing, which often involves cutting away a piece of the skull to expose the brain underneath and then carefully stimulating different areas. The idea is to determine whether the brain tissue can be cut away without leaving the patient in worse shape than before. To remove a tumor, for example, it may be reasonable to risk damaging the part of M1 that controls movements in one leg, but risk to other parts—say, the areas that control the tongue and allow swallowing and speaking—may call for extra caution.

Looking at the homunculus of Figure 2.13a, you'll notice that some body areas (the lips and hands, for example) seem grossly enlarged, while others (the arms and legs) seem shrunken. In other words, the physical size of a body area doesn't directly correspond to its relative size in the cortical map. In fact, if the homunculus were assembled into a figurine, it would look something like Figure 2.13b. The distortions aren't random. The parts of the body that are exaggerated on the homunculus are precisely those parts in which humans have the highest degree of fine motor control: fingers that are able to type, knit, and



(a)



(b)

Natural History Museum, London, UK/The Image Works

Figure 2.13 The homunculus corresponding to human motor cortex (a) By electrically stimulating each point of motor cortex (M1) and recording the evoked movements, researchers can map out the regions of the body controlled by each area of M1. If the homunculus so produced (here, for a male) is assembled into a model of a person (b), with the size of each body part determined by the relative amount of cortex devoted to it, the result is a figure with enlarged lips and hands—areas where human motor control is particularly precise.

play the piano; lips and tongue that move through the complicated contortions of speech; and facial muscles that display emotion. Other areas of the body that are physically larger, like the arms and legs, have proportionately less fine motor control, and so proportionately less area of motor cortex is devoted to them.

Electrical stimulation can be used not only to generate movements in individuals, but also to generate visual, auditory, and somatosensory sensations (by stimulating neurons in sensory cortices). It is also possible to evoke feelings of *déjà vu*, the illusion of feeling that a novel experience has happened before, by stimulating neurons within the temporal lobe. It is even possible to classically condition animals (as described in Chapter 1) by using one electrode to generate neural firing patterns that would occur during the sensation of a sound and pairing that with stimulation from a second electrode that provokes a reflexive motor response. This kind of "virtual reality" training is described in greater detail in Chapter 4.

Neural stimulation studies in patients and animal models have greatly increased our understanding of how neural activity is translated into behavior. The relatively new methods of *transcranial magnetic stimulation* (*TMS*) and *transcranial direct-current stimulation (tDCS)* now allow researchers to extend these kinds of studies to humans not undergoing brain surgery. TMS changes activity in cerebral cortex by generating strong magnetic pulses over the skull (Figure 2.14), and tDCS delivers low-level electrical current through electrodes

placed on the scalp. Both approaches activate large cortical networks rather than individual neurons. Depending on the level of stimulation, transcranial stimulation can either facilitate neural functions or disrupt them. Some recent work suggests that both TMS and TDCS can improve function in patients with memory disorders (Floel, 2014; Reis et al., 2008). Data from transcranial stimulation studies may be most useful when combined with results from other studies of neural stimulation in animals and from functional neuroimaging studies in humans to help build the most complete picture possible of which parts of the brain give rise to which kinds of behavioral changes.

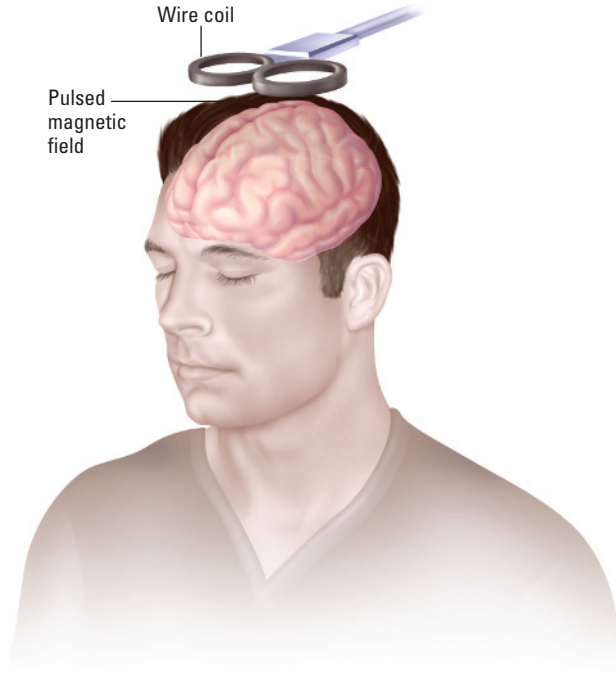


Figure 2.14 Using TMS to modulate cortical activity This technique enables researchers (1) to disrupt cortical activity in volunteers to temporarily simulate cortical lesions or, conversely, (2) to temporarily increase the probability that cortical neurons respond to inputs, thereby enhancing some cortical functions.

Chemical Control of Brain States

In addition to electrical and magnetic stimulation, a third method for manipulating neural activity is the use of **drugs**, chemical substances that alter the biochemical functioning of the body. For example, memory researchers have used the drug scopolamine to temporarily impair memory abilities by disrupting the actions of acetylcholine in the brain. Researchers may not always have a clear idea of why specific drugs enhance or hinder behavior, but it is clear that drugs can change neural activity, so it is no surprise that they can alter learning and memory processes.

drug. A chemical substance that alters the biochemical functioning of the body and in many cases affects the brain.

Drugs that work on the brain generally do so by altering synaptic transmission. The effects of the drug on behavior depend on which neurotransmitters are involved and whether their ability to carry messages across the synapse is enhanced or impaired.

Drugs can affect any of the four major processes of synaptic transmission described in Section 2.2—neurotransmitter release, activation of postsynaptic receptors, neurotransmitter inactivation, and neurotransmitter reuptake (depicted in Figure 2.10b):

1. Drugs can increase or decrease the ability of the presynaptic neuron to produce or release neurotransmitter. For example, amphetamines alter the function of neurons that produce the neurotransmitter dopamine, causing the neurons to release greater than normal quantities of dopamine. This means that postsynaptic neurons receive stronger and more frequent messages than normal. Because the dopamine system is involved in the processing of reward in the brain, the result may be feelings of pleasurable anticipation or excitement. (You will learn more about dopamine in Chapter 5, on operant conditioning.)
2. Drugs can increase or decrease the ability of postsynaptic receptors to receive the chemical message. For example, heroin and morphine are chemically very similar to a class of naturally occurring neurotransmitters called endogenous opioids. When heroin or morphine is released into the brain, molecules of the drug can activate the receptors normally activated by the endogenous opioids. In effect, the drugs "fool" the postsynaptic neuron into thinking that strong signals are being received from many presynaptic neurons. As a result, weak chemical messages that would not normally cause firing in postsynaptic neurons instead cause lots of neurons to fire. The endogenous opioids seem to be important in

Drugs that work on the brain generally do so by altering what?

how the brain processes and signals pleasure, most likely explaining why drugs that mimic endogenous opioids often cause intense feelings of pleasure (also discussed further in Chapter 5).

3. and 4. Drugs can alter the mechanisms for clearing neurotransmitter molecules out of the synapse. Some antidepressant medications (including the selective serotonin reuptake inhibitors, or SSRIs) work by reducing the rate at which serotonin is cleared from synapses. Thus, each time a presynaptic neuron releases serotonin molecules into the synapse, the molecules remain in the synapse longer, increasing their chance of activating a receptor and eliciting a reaction in the postsynaptic cell.

This list is just the beginning of the ways in which drugs can affect brain function. In addition, a drug can have more than one effect, and it can affect more than one neurotransmitter system. Some of the most commonly used drugs, including alcohol and nicotine, have been intensively studied. Yet although their effects on behavior are well documented, their effects on neurons and synaptic transmission are so varied that the precise mechanisms by which these drugs affect the neural substrates of learning and memory are not yet entirely clear.

Few pharmaceutical drugs have been developed specifically to affect learning and memory abilities (see "Learning and Memory in Everyday Life" on page 63 for efforts in this direction). More commonly, a drug's positive or negative effects on these abilities are considered side effects. For example, some types of general anesthesia administered to ease the pain of childbirth can also inadvertently "erase" a mother's memory of her baby being born.

Causing Changes in Neural Connections

synaptic plasticity. The ability of synapses to change as a result of experience.

Any physical change in neurons, or in the systems that support them such as glia and blood vessels, can affect how they communicate and how brain systems interact. Nevertheless, learning and memory researchers have focused almost exclusively on understanding the role of **synaptic plasticity**, the ability of synapses to change as a result of experience. The idea that connections between neurons change during learning was first popularized by Santiago Ramón y Cajal (1852–1934), a famous Spanish physiologist and anatomist. Specifically, Cajal theorized that learning involves strengthening or weakening connections between individual neurons (Ramón y Cajal, 1990 [1894]). This same basic idea was also proposed by William James, who as you may recall from Chapter 1, believed that changes in physical connections within the brain determined how memories were linked together.

But how exactly can the right connections between neurons be weakened or strengthened by learning experiences? One of neuroscience's most enduring insights regarding the neural substrates of learning came from Donald Hebb, a Canadian neuroscientist who studied under Karl Lashley. In one of the most often quoted passages in neuroscience, Hebb wrote: "When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place such that A's efficiency, as one of the cells firing B, is increased" (Hebb, 1949). In other words, if two neurons that meet at a synapse—we'll call them neuron A and

LEARNING AND MEMORY IN EVERYDAY LIFE

Can a Pill Improve Your Memory?

If you've ever studied for a difficult exam, you've probably wished for a pill that could make your brain function like a copy machine. Instead of reading, reviewing, and rehearsing, you could swallow the pill, read the material once, and have it encoded in your brain forever (or at least until the exam is over). Sounds like science fiction, right?

In fact, several companies, ranging from pharmaceutical giants to smaller biotech firms, are looking for a drug to improve memory in healthy people (Lynch, Palmer, & Gall, 2011; Monti & Contestabile, 2009). Some possible candidates are currently being tested on laboratory rats, and a few are even being tested in small groups of human volunteers. It remains to be seen which, if any, of these new drugs will be safe and effective.

Until a new generation of memory-boosting drugs becomes available, researchers continue to examine existing drugs, many already approved for the treatment of other illnesses, to see whether any might provide a memory boost in normal, healthy people. For example, several drugs used in treating Alzheimer's disease—including donepezil (Aricept)—increase brain levels of the neurotransmitter acetylcholine, which is abnormally low in people with Alzheimer's. These drugs can produce modest, temporary memory improvements in Alzheimer's patients, raising the possibility that they might also improve memory in healthy (or mildly impaired) adults (Whitehead et al., 2004). However, there is little evidence so far to suggest that the drugs can boost memory in otherwise healthy people (Beglinger et al., 2004; Stern & Alberini, 2013).

Another approach to finding memory-enhancing drugs is based on the fact that attention and concentration can increase the storage and retention of new information. Perhaps drugs that improve attention will also improve memory. Such attention-boosting drugs include modafinil (Provigil), which is used to treat sleep disorders, and methylphenidate (Ritalin), used to treat attention deficit hyperactivity disorder (ADHD). Many college students already pop Ritalin in an effort to boost studying or exam performance. But it's not clear that boosting attention beyond normal levels is necessarily good for memory. The jury is still out on whether these drugs improve memory in healthy humans (Mehta et al., 2000; Turner et al., 2003). The bottom line is that, so far, no pill can substitute for the hard work of learning. Instead of spending money on "brain-boosting" drugs of questionable efficacy and safety, healthy people are best advised to do their learning the old-fashioned way: by devoting the necessary time to study.

neuron B—often fire at nearly the same time, then the synapses between them should be strengthened, "wiring" the two neurons together. This would increase the probability that whenever neuron A became active, it would cause neuron B to become active, too. A shorthand version of this "rule" that neuroscientists often use is *neurons that fire together, wire together*.

Hebbian Learning

Learning that involves strengthening connections between neurons that work together is called **Hebbian learning**. Figure 2.15 shows a simple model of Hebbian learning. Eight hypothetical cortical neurons are shown, each with weak connections to surrounding neurons (Figure 2.15a). Now let's assume that some sensory stimulus evokes activation in a subset of these neurons that are tuned to features of this stimulus (solid circles in Figure 2.15a). As those neurons become active, they produce outputs that are transmitted to other nearby neurons. According to Hebb's rule—neurons that fire together, wire together—the connections between coactive neurons are strengthened as a result. Repeated coactivity of the same subset of neurons, in response to the same stimulus, has a cumulative effect, resulting in the strong connections (heavy lines) shown in Figure 2.15b. Thus, repeated exposure to a stimulus can strengthen connections within a distinctive subset of cortical neurons, and this subset can then provide an increasingly reliable basis for identifying the stimulus that is activating them. Changing the connections between cortical neurons creates a pattern that makes a repeated stimulus more likely to be recognized and distinguished from other stimuli.

Hebbian learning. The principle that learning involves strengthening the connections of coactive neurons; often stated as, "Neurons that fire together, wire together."

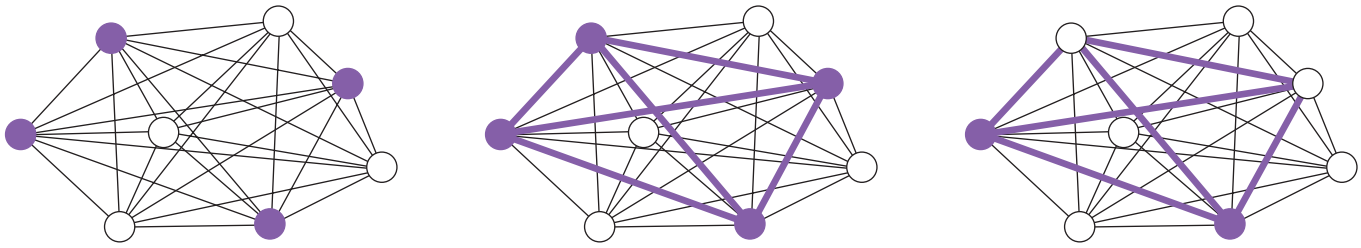


Figure 2.15 A simple model of Hebbian learning Circles correspond to cortical neurons, and lines denote connections between them. (a) Stimulus inputs activate a subset of the neurons (solid circles). (b) Connections between coactive neurons are strengthened (heavy lines). (c) After connections between coactive neurons have been established, an incomplete version of a familiar stimulus may activate just some of the neurons (solid circles) in the subset that represents the stimulus. Activation flows along the strengthened connections and ultimately retrieves the complete stimulus, resulting in the representation shown in (b).

Hebbian learning can also explain how repeated experiences can enhance the ability to recognize familiar stimuli (discussed further in Chapter 3). Suppose that once connections have been established between cortical neurons, the organism encounters an incomplete version of a familiar stimulus (Figure 2.15c). Only some of the subset of neurons that represents that familiar stimulus are activated at first (solid circles in Figure 2.15c), but the connections already established through repeated experiences will produce outputs that complete the familiar pattern, reconstructing Figure 2.15b. Similarly, recognition of distorted versions of a familiar stimulus, such as might occur when you meet an old friend who has dyed her hair, could also be facilitated by stored patterns encoded as connections between neurons that on previous occasions were simultaneously active.

According to Hebb, learning-related changes in synaptic connections between neurons are an automatic result of the neurons' mutual activity. We now know that Hebb was on the right track. But it was several more decades before technology advanced to the point where researchers gained the ability to directly control such experience-related changes in neural activity.

Long-Term Potentiation and Long-Term Depression

In the late 1960s, Terje Lømo was pursuing his doctoral degree in the lab of Per Andersen at the University of Oslo in Norway. Part of Lømo's research consisted of electrically stimulating the axons of presynaptic neurons that provided inputs to the hippocampus of a rabbit. He simultaneously recorded electrical activity produced by postsynaptic neurons within the hippocampus (Figure 2.16a). Normally, a certain amount of stimulation produced a certain level of response: a single weak stimulation would produce a low response in hippocampal neurons, and a strong burst of high-frequency stimulation (say, 100 stimulations in a second) would produce a more robust response. But to Lømo's surprise, the high-frequency stimulation also caused a lasting change in responding, so that hippocampal neurons would over-respond to subsequent weak stimulation (Figure 2.16b). This change could last for hours (Bliss & Gardner-Medwin, 1973; Bliss & Lømo, 1973; Lømo, 1966).

Imagine you have a brother who constantly torments you with his snide comments. Most of the time, you don't react. But one day he says something that's really over the top, and you respond with some strong language of your own. A few minutes later, before you've had a chance to calm down, he makes another little snide comment. Ordinarily, you might not have bothered to respond. But this time you haven't yet cooled down from the earlier explosion, so you lose

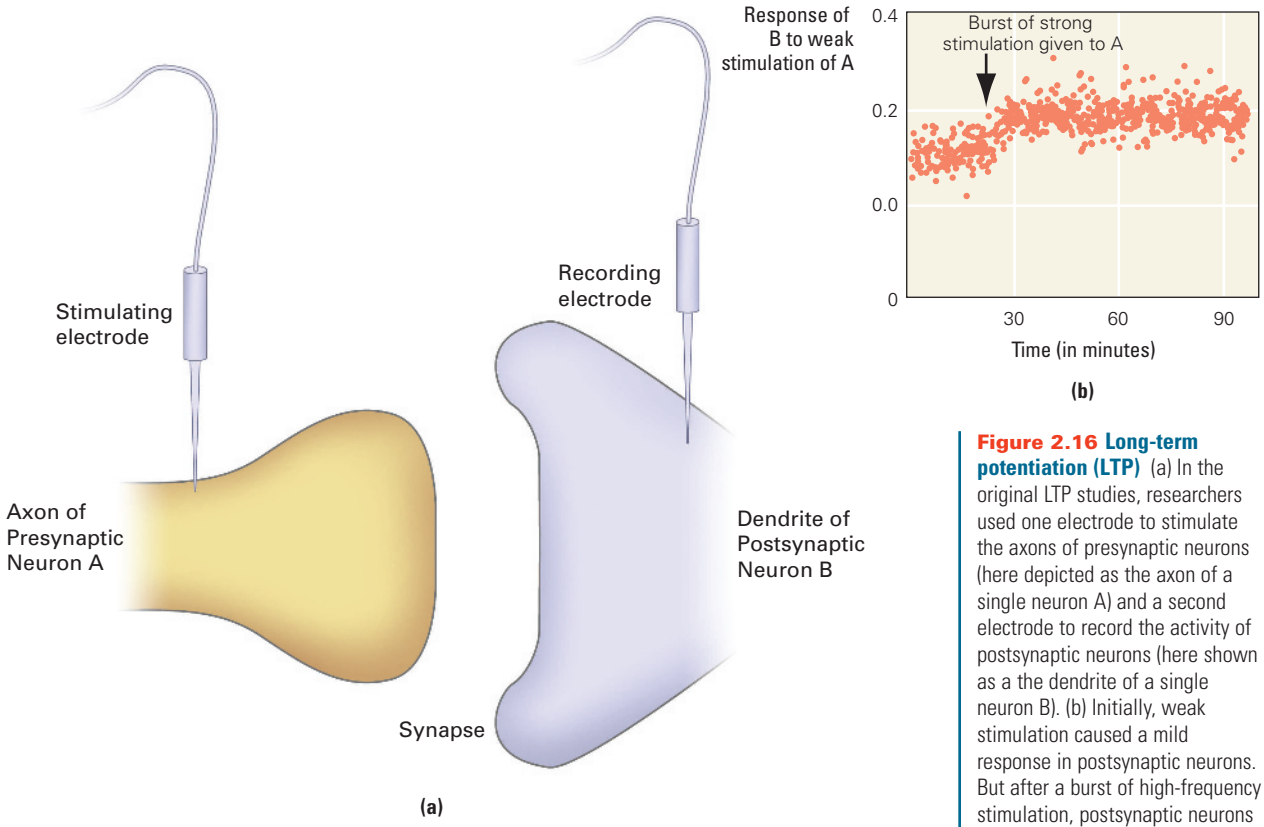


Figure 2.16 Long-term potentiation (LTP) (a) In the original LTP studies, researchers used one electrode to stimulate the axons of presynaptic neurons (here depicted as the axon of a single neuron A) and a second electrode to record the activity of postsynaptic neurons (here shown as a the dendrite of a single neuron B). (b) Initially, weak stimulation caused a mild response in postsynaptic neurons. But after a burst of high-frequency stimulation, postsynaptic neurons persistently responded more strongly to the weaker stimulation.

it again. Your prior anger has *potentiated* your response to a weak stimulus that normally wouldn't have evoked such a strong reaction.

Potentiation of a neuron by a strong stimulus is similar (except that the "irritation" can last much longer), making the neuron more likely to respond to any subsequent stimulus. This effect, in which synaptic transmission becomes more effective as a result of recent activity, came to be called **long-term potentiation (LTP)**. The reports by Lømo and his coworkers demonstrated that electrical stimulation could not only be used to cause neurons to change their activity but that these changes could last for hours or even days (Bliss & Gardner-Medwin, 1973; Bliss & Lømo, 1973). Since that time, LTP has become one of the most extensively investigated phenomena in the neuroscience of memory.

long-term potentiation (LTP). A process in which synaptic transmission becomes more effective as a result of recent activity; with long-term depression, widely believed to represent a form of synaptic plasticity that could be the neural mechanism for learning.

Despite intensive study of LTP in the decades since it was initially reported, many questions remain about exactly what changes occur to produce it, and how it relates to learning in more natural contexts. Perhaps postsynaptic neurons change to become more responsive to subsequent inputs. This would mean that when presynaptic neurons release neurotransmitters after strong stimulation, the postsynaptic neurons will have a heightened sensitivity to that neurotransmitter, producing the enhanced response seen in Figure 2.16b.

LTP may also involve changes to presynaptic neurons. This idea is controversial, because it isn't clear exactly how signals could travel backward across the synapse. But perhaps some kind of chemical—a *retrograde messenger*—could be released by postsynaptic neurons and diffuse across the synapse, causing an increase in the amount of neurotransmitter the presynaptic neurons release in the future. These changes might occur within a few minutes and last several hours. In addition, however, most researchers currently believe there are

components of LTP that take place over several hours and can last a lifetime. This would involve changes such as strengthening of existing synapses or even the building of new ones (Chen, Rex, Casale, Gall, & Lynch, 2007).

As excited as researchers were about the possibilities of LTP as a mechanism for learning and memory, they were aware of a significant remaining question. LTP represents a way to strengthen neural connections, but this alone isn't much use. If you think of the activity patterns of a neuron as being like an audio signal, then LTP corresponds to pumping up the volume of particular input patterns. But imagine an orchestra conductor who can only make the musicians play louder. Every symphony would be deafening by the time it ended! There has to be a way to turn the volume down as well as up. For LTP to be effective as a way to increase the strength of useful synapses, there would also have to be a process that can decrease the strength of less useful synapses.

long-term depression (LTD). A process in which synaptic transmission becomes less effective as a result of recent activity; with long-term potentiation, widely believed to represent a form of synaptic plasticity that could be the neural mechanism for learning.

Soon after Lømo and others' original reports, such a process was discovered (Dunwiddie & Lynch, 1978). **Long-term depression (LTD)**, also referred to as *synaptic depression*, occurs when synaptic transmission becomes *less* effective as a result of recent activity. One situation in which this happens is if presynaptic neurons are repeatedly active but the postsynaptic neurons do not respond. Neurons that fire together wire together, but connections between neurons that don't fire together weaken, a change that is believed to reflect a weakening in synapses. As with the synaptic changes in LTP, researchers have various ideas about how the weakening might occur: there may be a decrease in the responsiveness of postsynaptic neurons, a decrease in neurotransmitter release by presynaptic neurons, or long-term structural changes in the neurons and synapses. As with LTP, many of the details of LTD remain to be worked out. Scientists still have a long way to go to understand synaptic plasticity and its relation to learning and memory.

Test Your Knowledge

Synaptic Plasticity

Synaptic plasticity is one of the most researched phenomena in the field of neuroscience, yet many of its features remain poorly understood. Identify which of the following statements accurately describe what is known about synaptic plasticity. (Answers appear in the back of the book.)

1. Synaptic change can be produced through electrical stimulation.
2. Whenever firing patterns change in a neural circuit, synaptic change has occurred somewhere in the circuit.
3. Synaptic plasticity can weaken or strengthen connections between neurons.
4. Synaptic plasticity can be measured in humans with fMRI.
5. LTP is observed only in animals that have recently been learning.

Interim Summary

- Accidental brain lesions in humans have revealed much about how different brain regions function. Intentional brain lesions in animal models have similarly provided insights into how different regions contribute to learning and memory.
- Researchers can also use implanted electrodes to stimulate neurons into activity so that the sensations or responses that they evoke can be observed. Just as lesions can degrade memory abilities, stimulation can sometimes enhance memory.

- Drugs are chemicals that alter the biochemical functioning of the body. Drugs that affect the brain generally change neural activity by interfering with synaptic transmission.
- The ability of synapses to change with experience is called synaptic plasticity. Strengthening or weakening the connections between neurons can influence when they fire. Such changes in connections are thought to be a primary mechanism of memory formation.
- Long-term potentiation (LTP) occurs when synaptic transmission becomes more effective as a result of strong electrical stimulation of neurons.
- An opponent process to LTP, called long-term depression (LTD), occurs when synaptic transmission becomes less effective after neurons do not fire together.

Synthesis

We've covered a lot of ground in this chapter. We started with the basic geography of nervous systems, moved on to some key principles of how the various brain regions process different kinds of inputs and outputs, and ended by looking at how synapses can change over time.

If you get the feeling that, for all this information, there are still a frustrating number of unresolved questions about the neural substrates of learning and memory, you're absolutely correct. But this is also a time when neuroscientists have access to an unprecedented selection of techniques: neuroimaging and recording methods that allow visualization of brain activity at multiple scales in living organisms; advanced microscopes that make synapses, dendrites, and neurotransmitter-containing vesicles visible; and systems capable of recording single-cell activity from hundreds of neurons simultaneously. These tools, now in fairly routine use, didn't even exist a few decades ago.

In the following chapters, we dig deeper into the mechanisms that make learning and memory possible. The involvement of the hippocampus in these processes has been widely studied in humans and other animals. Consequently, this brain region is discussed in more chapters than any other part of the brain. Chapter 3 describes links between the hippocampus and spatial memories, Chapter 4 describes hippocampal contributions to eyeblink conditioning, and Chapter 7 describes the dramatic impacts of hippocampal damage on memories for facts and events. Hippocampal processing also contributes to generalization of learning (Chapter 6), emotional learning (Chapter 10), and the social transfer of information (Chapter 11). Intriguingly, the hippocampus is also one of the few regions in the mammalian brain where new neurons are born throughout adulthood, a process that may contribute to our ability to keep learning new information across a lifetime (Chapter 12).

Several regions of the cerebral cortex have also been shown to underlie various learning and memory capacities, and so discussion of cortical processing is likewise spread across multiple chapters. Changes in sensory and motor cortices associated with learning are described in Chapters 3, 6, and 8, while the roles of frontal and association cortex in memory formation and retrieval are reviewed in Chapter 7. Frontal cortex also is discussed extensively in Chapter 9, where it is related to the ability to juggle thoughts and memories and to voluntarily manipulate how memories are used.

Three other brain regions emphasized in the following discussions are the cerebellum, the basal ganglia, and the amygdala. The cerebellum has been studied extensively as a site of memory storage and processing in classical conditioning research (Chapter 4) and in relation to skill learning (Chapter 8). The basal

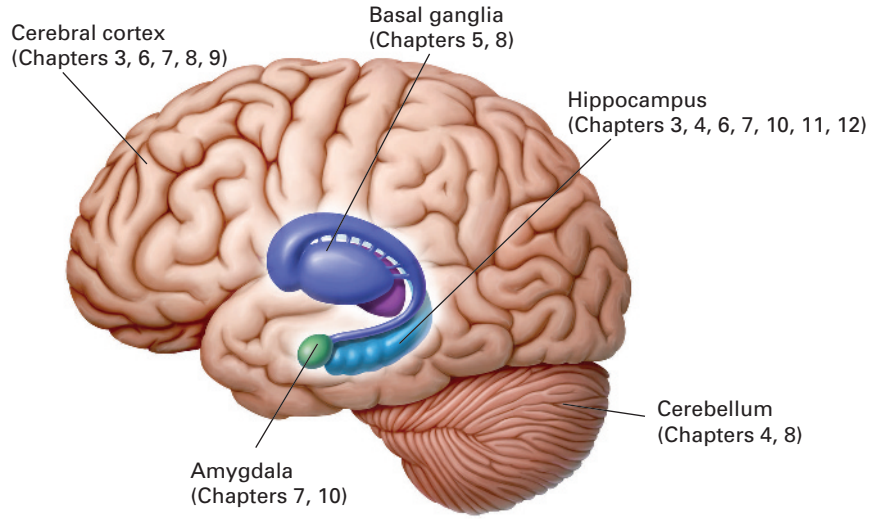


Figure 2.17 Overview of brain regions discussed in subsequent chapters The hippocampus, cortex, cerebellum, basal ganglia, and amygdala all contribute to learning and memory in different ways. Their roles are described in further detail in the chapters indicated.

ganglia are also implicated in skill learning, particularly when learning involves reinforcement (Chapter 5) and sensory-guided actions (Chapter 8). Finally, the amygdala is central to emotional learning, affecting how rapidly memories are formed (Chapter 10) and how long they last (Chapter 7). Figure 2.17 summarizes where each of these brain regions is discussed in the book.

We hope that the following chapters will engage all of these brain regions and more, enabling you to better encode and organize your own knowledge about learning and memory phenomena.

KNOW YOUR KEY TERMS

axon, *p. 41*
brainstem, *p. 38*
cell body, *p. 41*
central nervous system (CNS), *p. 37*
cerebellum, *p. 38*
cerebral cortex, *p. 38*
dendrite, *p. 41*
difference image, *p. 52*
diffusion tensor imaging (DTI), *p. 43*
drug, *p. 61*
electroencephalography (EEG), *p. 53*
engram, *p. 58*
enriched environment, *p. 44*
event-related potential (ERP), *p. 54*
frontal lobe, *p. 38*
functional magnetic resonance imaging(fMRI), *p. 53*
functional neuroimaging, *p. 52*
glia, *p. 42*
Hebbian learning, *p. 63*
lesion, *p. 43*
long-term depression (LTD), *p. 66*
long-term potentiation (LTP), *p. 65*
magnetic resonance imaging (MRI), *p. 43*
nervous system, *p. 37*
neuromodulator, *p. 51*
neuron, *p. 37*
neurophysiology, *p. 55*
neuropsychology, *p. 57*
neuroscience, *p. 36*
neurotransmitter, *p. 49*
occipital lobe, *p. 38*
parietal lobe, *p. 38*
peripheral nervous system (PNS), *p. 37*
phrenology, *p. 42*
positron emission tomography (PET), *p. 53*
postsynaptic, *p. 49*
presynaptic, *p. 49*
receptor, *p. 50*
reflex, *p. 46*
single-cell recording, *p. 55*
soma, *p. 41*
structural neuroimaging, *p. 43*
synapse, *p. 49*
synaptic plasticity, *p. 62*
temporal lobe, *p. 38*
theory of equipotentiality, *p. 58*

QUIZ YOURSELF

1. The brain and spinal cord together make up the _____. (p. 37)
2. Sensory receptors within your fingers and toes are part of your_____. (p. 37)
3. The temporal lobe, parietal lobe, occipital lobe, and frontal lobe are all subdivisions of the _____. (p. 38)
4. The _____ looks like a smaller brain hiding underneath the cerebral cortex. (p. 38)
5. _____ collect neurotransmitters released from a presynaptic neuron. (p. 49)
6. Cells other than neurons that are found throughout the brain include _____. (p. 42)
7. A major technique currently used to collect structural images of human brains is _____. (p. 43)
8. The fact that by nature babies placed underwater do not inhale water is an example of a(n) _____. (p. 46)
9. Neurons in the _____ play an important role in the generation and control of motor responses in humans. (p. 38–39)
10. The prototypical connections between neurons are between _____ and _____. (p. 41)
11. A(n) _____ is a hypothetical physical change in neurons that forms the basis of a memory. (p. 58)
12. _____ are a technique for identifying specific brain regions that are more or less active during the performance of particular memory tasks. (p. 52)
13. If electrodes are attached to a person's head, it is probably because _____ recordings are being collected. (p. 53)
14. One method for activating neurons in the cerebral cortex of humans without requiring surgery is _____. (p. 60)
15. Chemical substances that when brought into the body can change how long neurotransmitters can activate receptors in a synapse are called _____. (p. 61)
16. When connected neurons are firing at the same time, _____ can result. (p. 62–66)

Answers appear in the back of the book.

CONCEPT CHECK

1. In addition to learning to salivate whenever they heard a bell, some of Pavlov's dogs learned to salivate whenever Pavlov walked into the room. Use the concepts of synaptic plasticity and Hebbian learning to explain why this might have occurred. What region(s) of a dog's cortex might have changed as a result of this learning?
2. Neuroimages of different individuals performing the same task often differ greatly in the brain regions shown to be activated. Does this mean that the brains of these individuals function differently? If not, why not?
3. Drugs that block LTP in the hippocampus impair learning in some tasks but facilitate learning in other tasks. Similarly, some researchers have correlated LTP-like effects with learning in a variety of tasks, whereas others have observed learning in the absence of these LTP effects. What does this tell us about the relationship between LTP and learning?
4. Carbon monoxide poisoning can damage many different parts of the brain, resulting in many different kinds of deficits—for example, severe impairments in language or an inability to recognize objects. Describe one way a neuropsychologist could determine what part(s) of the brain might have been damaged.
5. Lashley's findings from lesion experiments in rats suggest that the brain can function when only part of the cerebral cortex is available. Additionally, invertebrates have been learning successfully for millions of years with less than 1% of the total neurons mammals have. What does this information imply about the role of the cerebral cortex in learning and memory?

Answers appear in the back of the book.