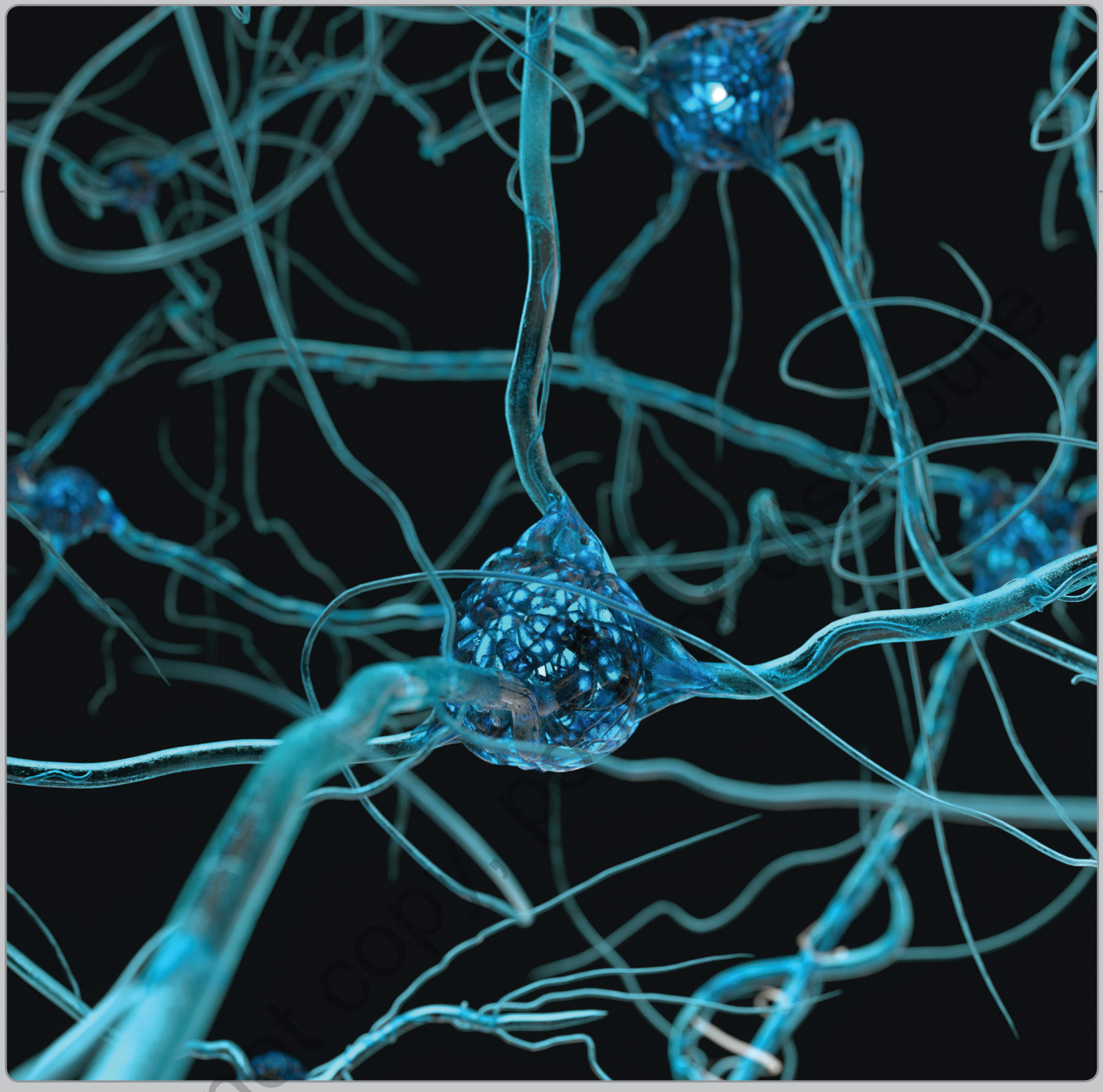
Part I

Neural Foundations of Behavior

The Basic Equipment



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2 Communication Within the Nervous System

After reading this chapter, you will be able to

- **2.1** Identify the cells of the nervous system.
- **2.2** Name the structures of neurons.
- **2.3** Compare the functions of sensory, motor, and interneurons.
- **2.4** Understand the roles of different types of glial cell.
- **2.5** Explain the roles of ions and the cell membrane in nervous system communication.
- **2.6** Explain how neurotransmitters are involved in communication between neural cells.
- **2.7** Discuss how neurons work together to generate your experiences of the world.
- **2.8** Illustrate the ways in which excitation and inhibition are important to the functioning of the nervous system.

Things were looking good for Jim and his wife. She was pregnant with their first child, and they had just purchased and moved into a new home. After the exterminating company treated the house for termites by injecting the pesticide chlordane under the concrete slab, Jim noticed that the carpet was wet and there was a chemical smell in the air. He dried the carpet with towels and thought no more about it, not realizing that chlordane can be absorbed through the skin. A few days later, he developed headaches, fatigue, and numbness. Worse, he had problems with memory, attention, and reasoning. His physician referred him to the toxicology research center of a large university medical school. His intelligence test score was normal, but the deficiencies he was reporting showed up on more specific tests of cognitive ability. Jim and his wife had to move out of their home; at work, he had to accept reduced responsibilities because of his difficulties in concentration and adapting to novel situations. The chlordane had not damaged the structure of his brain as you might suspect, but it had interfered with the functioning of the brain cells by impairing a mechanism called the sodium-potassium pump (Zillmer & Spiers, 2001). Jim's unfortunate case reminds us that the nervous system is as delicate as it is intricate. Only by understanding how it works will we be able to appreciate human behavior, to enhance human performance, and to treat behavioral problems such as drug addiction and psychosis.

FIGURE 2.1 Estimated Numbers of Neurons in the Brain and Spinal Cord.

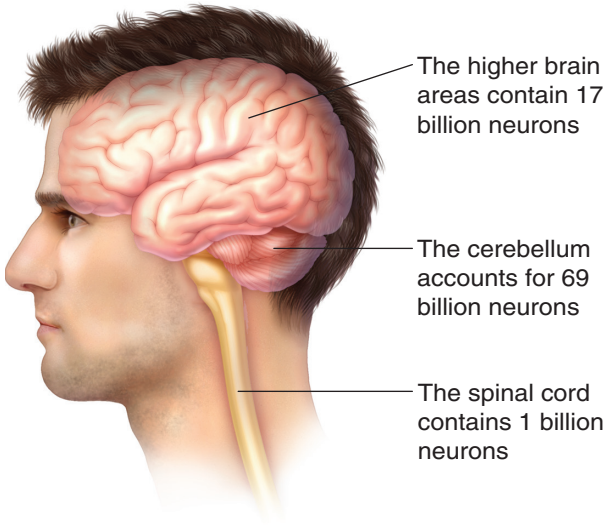
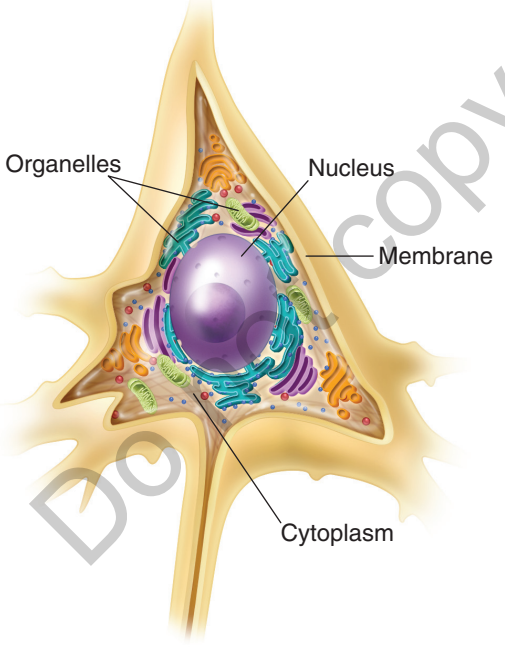


FIGURE 2.2 Cell Body (Soma) of a Neuron.

Part of the membrane has been removed to show interior features.



The Cells That Make Us Who We Are

To understand how the brain works, you must first have at least a basic understanding of the two categories of cells that carry messages back and forth in the brain and throughout the rest of the body. *Neurons* convey sensory information into the brain; carry out the operations involved in thought, feeling, and action; and transmit commands out to the body to control muscles and organs. It is estimated that there are about 86 billion neurons in the human brain (Figure 2.1; Azevedo et al., 2009). This means that there are more neurons in your brain than stars in our galaxy. But as numerous and as important as they are, neurons make up only half of the brain's cells (von Bartheld, Bahney, & Herculano-Houzel, 2016). There are also almost as many glial cells and, as we will see later in the chapter, they are almost as important.

Neurons

Neurons are responsible for all the things we do—our movements, our thoughts, our memories, and our emotions. It is difficult to believe that anything so simple as a cell can measure up to this task, and the burden is on the neuroscientist to demonstrate that this is true. As you will see, the neuron is deceptively simple in its action but impressively complex in its function.

BASIC STRUCTURE: THE MOTOR NEURON

First, let's look inside a neuron, because we want to show you that the neuron is a cell, very much like other cells in the body. Figure 2.2 is an illustration of the most prominent part of the neuron, the *cell body* or soma. The cell body is filled with a liquid called cytoplasm and contains a number of *organelles*. The largest of these organelles is the *nucleus*, which contains the cell's chromosomes. Other organelles are responsible for converting nutrients into fuel for the cell, constructing proteins and lipids, and removing waste materials. So far, this could be the description of any cell; now, let's look at the neuron's specializations that enable it to carry out its unique role. Figure 2.3 illustrates a typical neuron. We use "typical" guardedly here, because there are three major kinds of neurons and many variations within those types. The figure illustrates a *motor neuron*, which carries commands to the muscles and organs. It is particularly useful for demonstrating the structure and functions that all neurons have in common.

Dendrites are extensions that branch out from the cell body to receive information from other neurons. Their branching structure allows them to collect information from many neurons. The *axon* extends like a tail from the cell body and carries information to other locations, sometimes across great distances. The myelin sheath that wraps around the axon supports the axon and provides other benefits that we will consider later. Branches at the end of the axon culminate in swellings called *axon terminals*. The terminals contain chemical

? What are the parts of the neuron?

neurotransmitters, which the neuron releases to communicate with a muscle, an organ, or the next neuron in a chain. In our examples, we will talk as if neurons form a simple chain, with one cell sending messages to a single other neuron, and so on; in actuality, a single neuron receives input from many neurons and sends its output to many others.

Neurons are usually so small that they can be seen only with the aid of a microscope. The cell body is the largest part of the neuron, ranging from 0.005 to 0.1 millimeter (mm) in diameter in mammals. (In case you are unfamiliar with metric measurements, a millimeter is about the thickness of a dime.) Even the giant neurons of the squid, favored

FIGURE 2.3 Components of a Neuron.

The illustration is of a multipolar motor neuron.

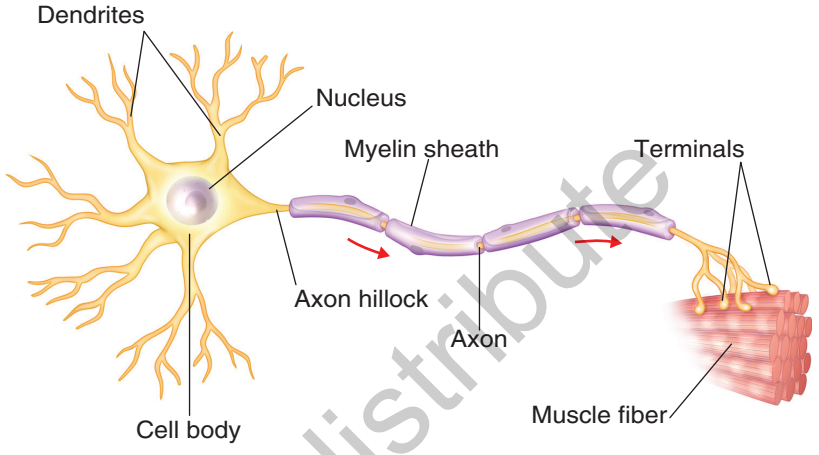
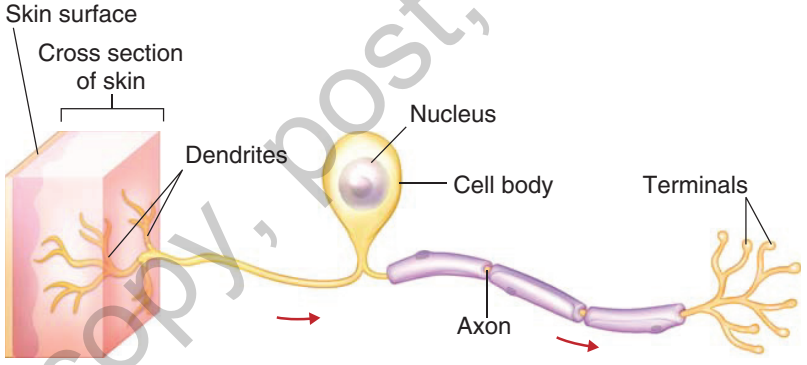


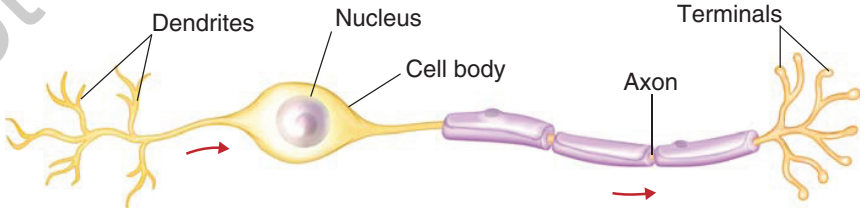
FIGURE 2.4 Sensory Neurons and an Interneuron.

Compare the location of the soma in relation to the dendrites and axon in these neurons and in the motor neuron.

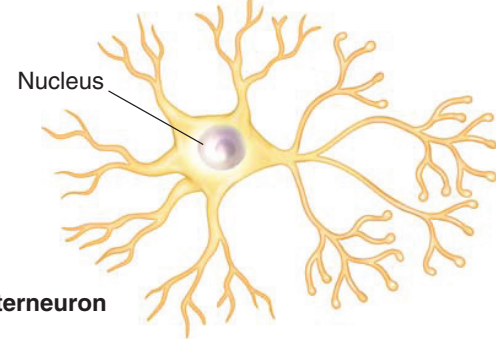
Carolina Hrejsa/Body Scientific Intl.



(a) Unipolar neuron (sensory)



(b) Bipolar neuron (sensory)



(c) Interneuron

by researchers for their conveniently large size, have axons that are only 1 mm in diameter. Typical axons are smaller; in mammals, they range from 0.002 to 0.02 mm in diameter. Axons may be as short as 0.1 mm or as long as 30 m in the blue whale (D. H. Smith, 2009).

OTHER TYPES OF NEURONS

The second type of neuron is the sensory neuron. *Sensory neurons* carry information from the body and the outside world into the brain and spinal cord. Motor and sensory neurons have the same components, but they are configured differently. A motor neuron's axon and dendrites extend in several directions from the cell body, which is why it is called a *multipolar* neuron. Sensory neurons can be either *unipolar* or *bipolar*. The sensory neuron in Figure 2.4a is called a unipolar neuron because the single short stalk from the cell body divides into two branches, with dendrites on one side and the axon and terminals on the other. (In the pseudounipolar subtype, both connections to the cell body are axons; that's because its sensory information must travel over a longer distance, from the periphery of the body to the spinal cord and the brain.) Bipolar neurons have an axon on one side of the cell body and a dendritic process on the other (Figure 2.4b). Motor and sensory neurons are specialized for transmission over long distances; their lengths are not shown here in the same scale as the rest of the cell.

The third type is neither motor nor sensory. *Interneurons* connect one neuron to another in the same part of the brain or spinal cord. Notice in Figure 2.4c that this neuron is also multipolar, but its axon appears to be missing; for some interneurons, this is so, and when they do have axons, they are often so short that they are indistinguishable from dendrites. Because interneurons make connections over very short distances, they do not need the long axons that characterize their motor and sensory counterparts. In the spinal cord, interneurons bridge sensory neurons and motor neurons to produce a reflex. In the brain, they connect adjacent neurons to carry out the complex processing that the brain is noted for. Considering the major roles they play, it should come as no surprise that interneurons are by far the most numerous neurons.

The different kinds of neurons operate similarly; they differ mostly in their shape, which fits them for their specialized tasks. We will examine how neurons work in the next few sections. The types of neurons and their characteristics are summarized in Table 2.1.

THE NEURAL MEMBRANE AND ITS POTENTIALS

The most critical factor in the neuron's ability to communicate is the membrane that encloses the cell. The membrane is exceptionally thin—only about 4 nanometers (billionths of a meter) thick—and is made up of lipid (fat) and protein (van Meer, Voelker, & Feigenson, 2008; Figure 2.5). Each lipid molecule has a "head" end and a "tail" end. The heads of the molecules are water soluble, so they are attracted to the seawater-like fluid around and inside cells. The tails are water insoluble, so they are repelled by the fluid. Therefore, as the heads orient toward the fluid and the tails orient away from the fluid, the molecules turn their tails toward each other and form a double-layer membrane.

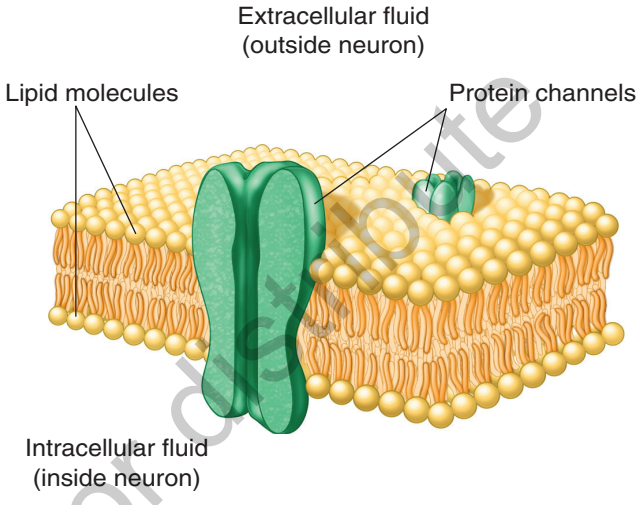
TABLE 2.1 The Major Types of Neurons.

TYPE	FUNCTION	FORM AND SOMA LOCATION	DESCRIPTION
Motor	Conducts messages from brain and spinal cord to muscles and organs	Multipolar; central nervous system	Axon, dendrites extend in several directions from cell body
Sensory	Carries information from body and world to brain and spinal cord	Unipolar; peripheral nervous system, cranial nerves	Single short stalk from cell body divides into two branches
		Bipolar; peripheral nervous system	Axon and dendritic processes are on opposite sides of cell body
Interneuron	Conducts information between neurons in same area	Multipolar; central nervous system	Has short or no axon; communicates locally (with nearby neurons)

The membrane not only holds a cell together but also controls the environment within and around the cell. Some molecules, such as water, oxygen, and most gases, can diffuse through the membrane freely. Many other substances are barred from crossing the membrane. Still others are allowed limited passage through protein channels (shown in the figure in green) that open and close under specific circumstances. This selective permeability contributes to the most fundamental characteristic of neurons, *polarization*, which means that there is a difference in electrical charge between the inside and outside of the neuron. A difference in electrical charge between two points, such as the poles of a battery or between the inside and outside of a neuron, is also called a *voltage*.

FIGURE 2.5 Cross Section of the Cell Membrane of a Neuron.

Notice how the lipid molecules form the membrane by orienting their heads toward the extracellular and intracellular fluids.



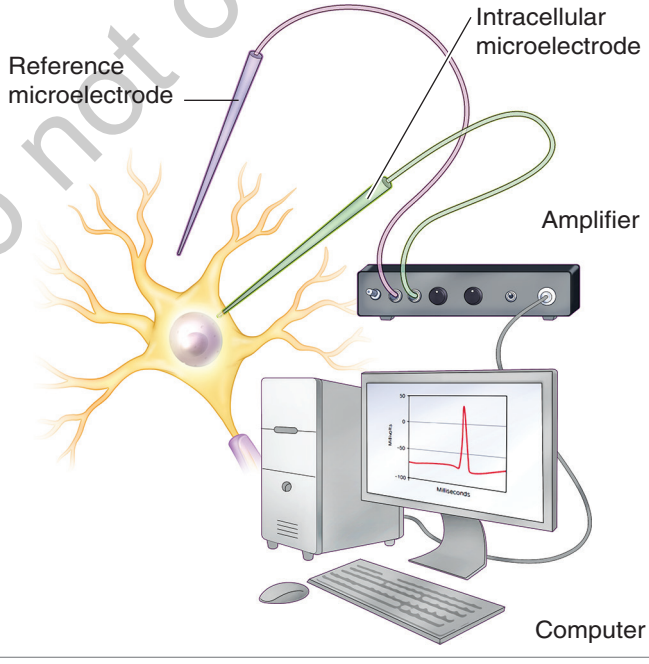
The Resting Potential. Just as you can measure the voltage of a battery, you can measure a neuron's voltage (Figure 2.6). By arbitrary convention, the voltage is expressed as a comparison of the inside of the neuron with the outside. The difference in charge between the inside and outside of the membrane of a neuron at rest is called the *resting potential*. This voltage is negative and varies anywhere from –40 to –80 millivolts (mV) in different neurons but is typically around –70 mV. You should understand that neither the inside of the neuron nor the outside has a voltage, because a voltage is a *difference* and is meaningful only in comparison with another location. Note that this voltage is quite small—the voltage of a standard 1.5-V battery is 25 times greater. No matter; we're moving information, and very little power is required.

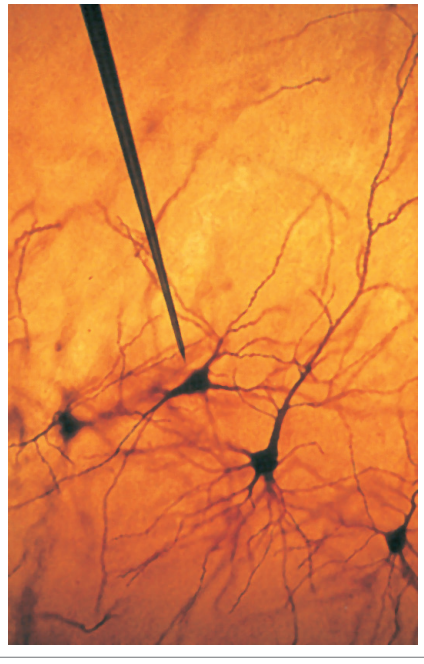
? What accounts for the resting potential?

The resting potential is due to the unequal distribution of electrical charges on the two sides of the membrane. The charges come from *ions*, atoms that have lost or gained one or more electrons.

FIGURE 2.6 Recording Potentials in a Neuron.

Potentials are being recorded in the axon of a neuron, with an electrode inside the cell and one in the fluid outside. Due to the size of neurons, the electrodes have microscopically small tips. On the right, a highly magnified view shows the size of a microelectrode relative to that of neurons. Electrodes for recording inside neurons are even smaller.

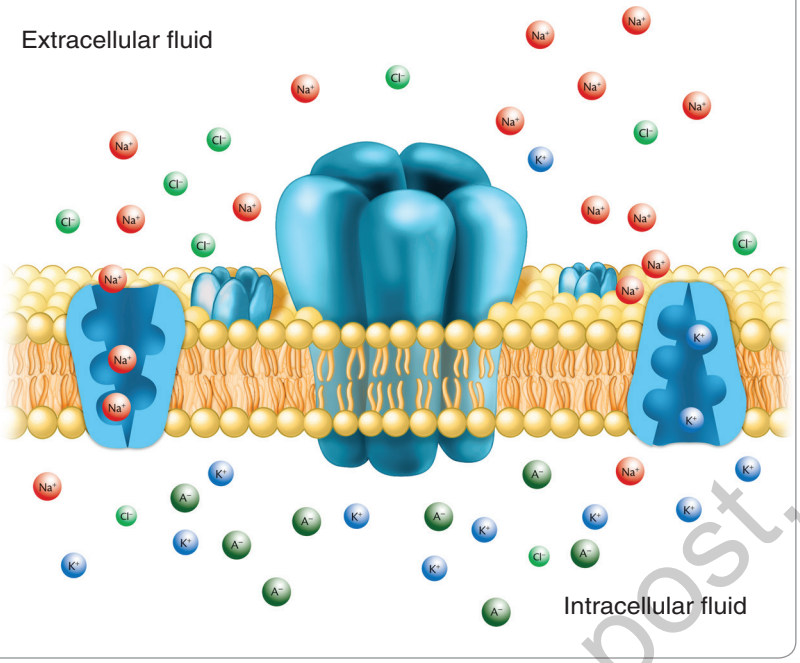




Right Photo: Bob Jacobs, Colorado College

FIGURE 2.7 Distribution of Ions Inside and Outside the Resting Neuron.

Ions on the outside are mostly Na^+ (red) and CL^- (green) ions; inside, the ions are mostly K^+ ions (blue) and organic anions (dark green). In the middle of the membrane is an ion channel, which is closed and not allowing ions through; on the left, a sodium-potassium pump is discharging three Na^+ ions outside the neuron, while on the right, an identical pump is returning two K^+ ions to the inside.



Sodium ions (Na^+) and potassium ions (K^+) are positively charged. Chloride ions (Cl^-) are negative, as are certain proteins and amino acids that make up the organic anions (A^-). The fluid outside the neuron contains mostly Na^+ and Cl^- ions, and the ions inside the neuron are mostly K^+ and A^- (Figure 2.7). The inside of the neuron has more negative ions than positive ions, whereas the ions on the outside are mostly positive, and this makes the resting potential negative.

If you remember from grade-school science that molecules tend to diffuse from an area of high concentration to one of low concentration, then you are probably wondering how this imbalance in ion distribution can continue to exist. In fact, two forces do work to balance the location of the ions. Because of the *force of diffusion*, ions tend to move through the membrane to the side where they are less concentrated. And as a result of *electrostatic pressure*, ions are repelled from the side that is similarly charged and attracted to the side that is oppositely charged.

In spite of these two forces, a variety of other influences keep the membrane polarized. Both forces would move the organic anions out, but they are too large to pass through the membrane. Their negative charge then repels the chloride ions, so the force of diffusion is unable to move those ions inside. As a result, the "real player" then becomes the potassium ions. Potassium's force of diffusion is stronger than its electrostatic pressure, and although the potassium and sodium channels are both closed during resting, potassium can slip through the membrane itself more readily than the other ions.

Another significant contributor to polarity is the *sodium-potassium pump*, which consists of large protein molecules that move sodium ions through the cell membrane to the outside and potassium ions back inside. It moves three sodium ions out for every two potassium ions it moves inside, which helps keep the inside of the membrane more negative than the outside. The pump's operation is a metabolic process, which means that it uses energy; in fact, it accounts for an estimated 40% of the neuron's energy expenditure. But you will soon see that this energy is well spent, because the resting potential stores the energy to power the action potential, the major signal in the nervous system.

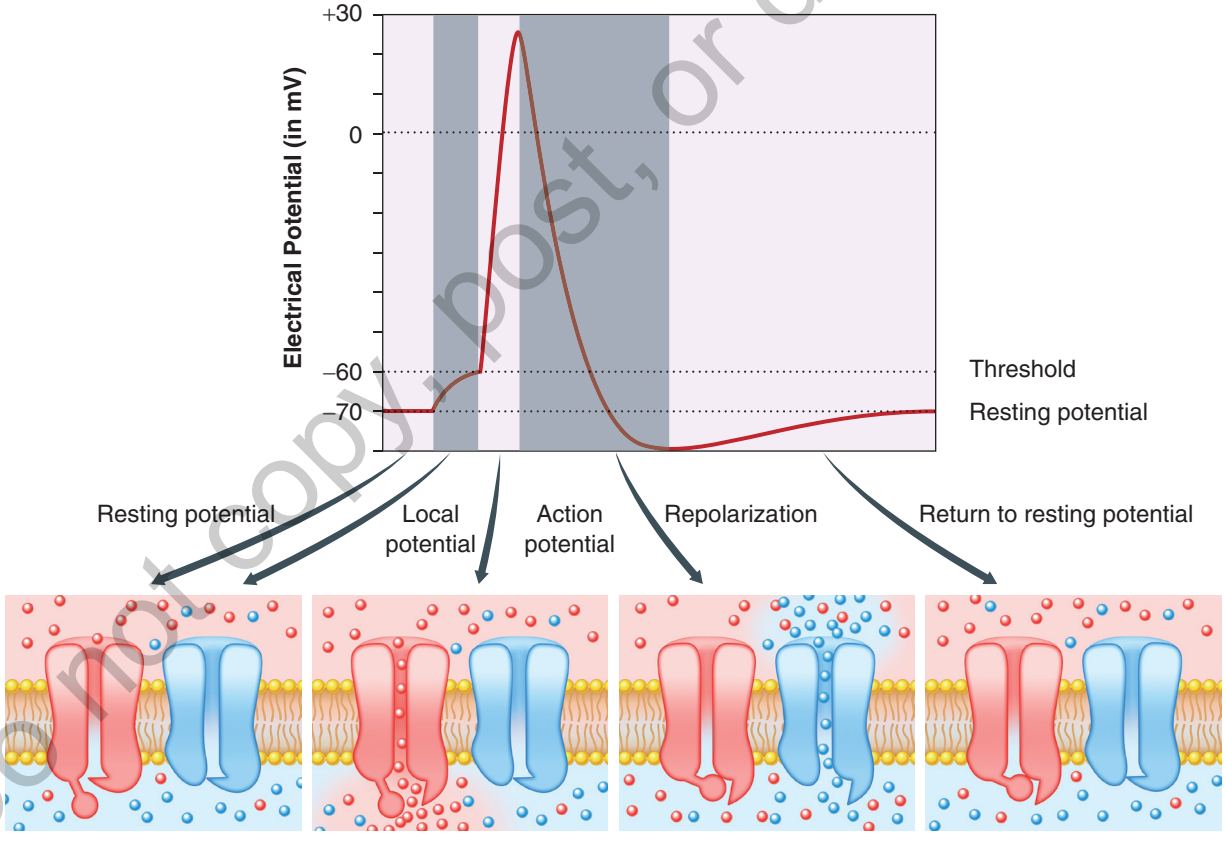
Ion Channels and Local Potentials. Before we move on, we need a better understanding of how the ion channels work. These are pores in the membrane formed by proteins, and they gate the flow of ions between the extracellular and intracellular fluids. Chemically gated channels can be opened by ligands (neurotransmitters or hormones), and electrically gated channels are opened by a change in the electrical potential of the membrane.

A neuron is usually stimulated by inputs that arrive on the neuron's dendrites and/or cell body from another neuron or from a sensory receptor. The effect may be excitatory or inhibitory, depending on the ligand and the characteristics of the receptors. An excitatory signal causes a slight partial depolarization, which means that the polarity in a small area of the membrane is shifted toward zero. This partial depolarization disturbs the ion balance in the adjacent membrane, so the disturbance flows down the dendrites and across

the cell membrane. This looks at first like the way the neuron might communicate its messages through the nervous system; however, because a partial depolarization is decremental—it dies out over distance—it is effective over only very short distances. For this reason, the partial depolarization is often called the *local potential*. The ion channels in the axon are electrically gated, and they have unique physical properties. If the local potential exceeds the threshold for activating those channels, typically about 10 mV more positive than the resting potential, it will initiate an action potential.

Action Potentials. The *action potential* is an abrupt depolarization of the membrane that allows the neuron to communicate over long distances. The voltage across the resting neuron membrane is stored energy, just as the term resting *potential* implies. Imagine countless sodium ions being held outside the neuron against the combined forces of diffusion and electrostatic pressure (Figure 2.8a). A stimulus that partially depolarizes a segment of membrane causes voltage-gated sodium ion channels to open; this allows nearby sodium ions to rush into the axon at a rate 500 times greater than normal (Figure 2.8b). They are propelled into the cell's interior so rapidly that the movement is often described as explosive. A small area

FIGURE 2.8 Ion Movement and Voltages During the Neural Impulse.



(a) Sodium channels (red) and potassium channels (blue) are closed and the membrane is at resting potential. Arrival of a local potential partially depolarizes the membrane but does not cause the channels to open unless it reaches threshold.

(b) As the local potential reaches the neuron's threshold, the sodium channels' activation gates open. Sodium ions (red) rush in, producing an action potential. The membrane in that area depolarizes and overshoots to positive.

(c) Sodium channels' inactivation gates close. Potassium channels' activation gates open; potassium ions (blue) move out, repolarizing the membrane. Polarity overshoots beyond resting potential.

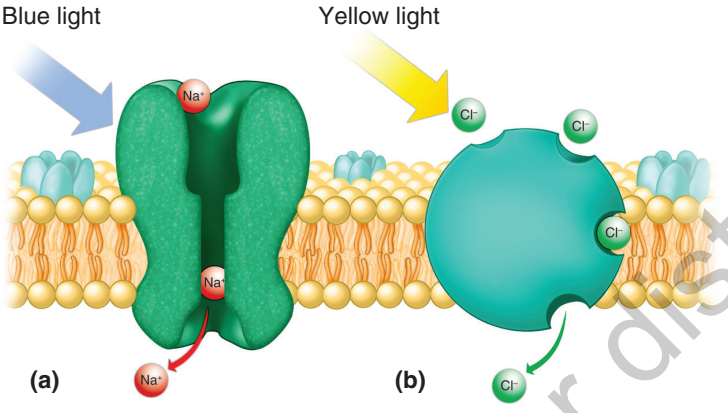
(d) Potassium channels close. The "excess" displaced ions drift away and the potential returns to resting level. (The sodium channel gates will return to their original state later.)

A FURTHER LOOK

Targeting Ion Channels

Modified Membrane Enables Light Control of Neuron Activity.

Stories of Brain & Behavior



(a) Blue light activates a channel from green algae; the channel allows positive ions to flow inward, triggering neural impulses. (b) Yellow light activates a chloride pump from bacteria; chloride ions hyperpolarize the neuron.

Source: Adapted from "Controlling Neural Circuits With Light," by M. Häusser and S. L. Smith, 2007, *Nature*, 446, 617–619 (Figure 1a, p. 617).

The Japanese delicacy fugu, or puffer fish, produces an exciting tingling sensation in the diner's mouth; improperly prepared, it causes numbness and weakness and, in some cases, a paralysis of the respiratory muscles that has claimed the lives of hundreds of culinary risk takers. The fish's natural poison, tetrodotoxin (TTX), blocks sodium channels and prevents neurons from firing (Siegelbaum & Kandel, 2013). Researchers are examining TTX as a potential replacement for opiate painkillers (Gorey, 2019; Nieto et al., 2012), so this dangerous toxin might lead to new treatments for chronic pain. Other *neurotoxins* (neuron poisons) are found in snake venoms, which block sodium, potassium (Benoit & Dubois, 1986; Fertuck & Salpeter, 1974), or calcium channels, and scorpion venom, which keeps sodium channels open, prolonging the action potential (Catterall, 1984; Chuang, Jaffe, Cribbs, Perez-Reyes, & Swartz, 1998; Pappone & Cahalan, 1987).

Interfering with neuron functioning can be useful, though; for example, most local anesthetics prevent neuron firing by blocking sodium channels (Ragsdale, McPhee, Scheuer, & Catterall, 1994), and some general anesthetics hyperpolarize the neuron by opening potassium channels and allowing the potassium ions to leak out (Nicoll & Madison, 1982; A. J. Patel et al., 1999). The cone snail of the South Seas can penetrate a wet suit with its proboscis and inject toxins that will kill a human in half an hour, but the various species' thousands of toxins that target sodium, potassium, or calcium channels or block neurotransmitter receptors are in demand by researchers developing pain relievers and drugs for preventing heart attacks and epilepsy (L. Nelson, 2004; Oliviera & Teichert, 2007).

An exciting new research strategy known as *optogenetics* allows researchers to create light-responsive channels (as well as receptors) in neurons so that they can be controlled by light. Different types of channels are triggered by different wavelengths of light, which allows the researcher either to accelerate or to inhibit firing. The procedure is being used to understand the circuitry in a variety of behaviors and brain processes and is showing potential for use in therapeutic procedures.

inside the membrane becomes fully depolarized to zero; the potential even overshoots to around +30 or +40 mV, making the interior at that location temporarily positive.

Just as abruptly as the neuron "fires," it begins to recover its resting potential. At the peak of the action potential, voltage sensors in the sodium channels detect the depolarization and close a gate, inactivating the channel and preventing further sodium ion influx (Catterall, 2010). The depolarization also causes voltage-gated potassium ion channels to open; the positive charge and the higher concentration of potassium ions inside the membrane combine to force potassium ions out. This outward flow of positive potassium ions lowers the axon voltage to its resting potential and sometimes a bit beyond (Figure 2.8c). In total, the action potential lasts about 1 millisecond (one thousandth of a second); the actual duration varies among individual neurons. (Obviously, these channels are what make the neuron operate; A Further Look (page 28) describes how they are exploited by nature and in research and medicine.)

Only a relatively few ions very near the two sides of the membrane have participated in the action potential; these dislocated ions quickly diffuse into the surrounding fluid, and the membrane potential returns to its resting level (Figure 2.8d). Eventually, though, the ions must be returned to their original locations, or the neuron cannot continue firing; the sodium-potassium pump takes care of this. (Perhaps you can see now why Jim was in such a bad way after his bout with chlordane.)

? What is the role of the sodium-potassium pump following an action potential?

The depolarization that occurs during the action potential triggers nearby sodium channels to open as well. Thus, a new action potential is triggered right next to the first one. That action potential in turn triggers another farther along, creating a chain reaction of action potentials that move through the axon; thus, a signal flows from one end of the neuron to the other. Nothing physically moves down the axon. Instead, a series of events occurs in succession along the axon's length, much as a line of dominoes standing on end knock each other over when you tip the first one. When the action potential reaches the terminals, they pass the signal on to the next neuron in the chain (or to an organ or a muscle). The transmission of signals from neuron to neuron is covered later; for now, the action potential needs to be examined a bit further.

The action potential differs in two important ways from the local potential that initiates it. First, the local potential is a *graded potential*, which means that it varies in magnitude with the strength of the stimulus that produced it. The action potential, by contrast, is *ungraded*; it operates according to the *all-or-none law*, which means that it occurs at full strength or it does not occur at all. A larger graded potential does not produce a larger action potential; like the fuse of a firecracker, the action potential depends on the energy stored in the neuron, in this case, due to the difference in ion concentrations between the two sides of the membrane. A second difference is that the action potential is *nondecremental*; it travels down the axon without any decrease in size, propagated anew and at full strength at each successive point along the way. The action potential thus makes it possible for the neuron to conduct information over long distances.

? How is an action potential different from a graded potential?

However, because the action potential is all-or-none, its size cannot carry information about the intensity of the initiating stimulus. One way stimulus intensity is represented is in the number of neurons firing. The voltage sensitivity of sodium channels varies among neurons, resulting in different thresholds; a more intense stimulus will recruit firing in neurons with higher thresholds and, therefore, in more neurons. There is, though, a way in which the individual neuron can encode stimulus strength, as you will see in the discussion of refractory periods.

REFRACTORY PERIODS

? What are the absolute and relative refractory periods?

If you remember a few paragraphs back, we stated that the flow of an action potential down the axon was like knocking down a line of dominoes. And just as you must go through and

reset the dominoes so that they can fall again, the ion channels must be reset before the neuron can fire again. During the action potential and initial recovery, the sodium ion channels are open and unresponsive to further stimulation, no matter how intense; this time is referred to as the *absolute refractory period*. This delay in responsiveness has two important effects. First, the 1- to 2-millisecond duration of the absolute refractory period limits how fast the neuron can generate new action potentials; a study of cortical *fast-spiking neurons* found maximal rates of 453 per second in humans, 611 in monkeys, and 342 in mice (B. Wang et al., 2016). Second, because the ion channels behind the action potential are still recovering, the impulse can propagate only down the axon toward the dendrites, not back toward the cell body. This makes neural transmission unidirectional, which has the secondary effect of preventing the neuron from "locking up." If recovery were immediate, activity would self-propagate in both directions from an ongoing action potential; this would result in impulses moving repeatedly back and forth along the axon, which would block the ability to respond to newly arriving messages.

At the end of the absolute refractory period, the sodium channels have closed, so the neuron is able to fire again. But the potassium channels remain open for an additional 3 or 4 milliseconds, and as potassium ions continue to exit the neuron, the polarity is driven slightly more negative than the resting potential (the "dip" in Figure 2.8). During the resulting *relative refractory period*, another action potential can be generated but only by a stronger-than-threshold stimulus. A stimulus that is slightly greater than this temporarily higher threshold will cause the neuron to fire again before the end of the relative refractory period; with progressively stronger stimuli, the neuron will fire increasingly earlier and, therefore, at a higher rate. Thus, the axon encodes stimulus intensity not in the size of its action potential but in its firing rate, an effect called the *rate law*.

Glial Cells

Glial cells are nonneural cells that provide a number of supporting functions to neurons. The name *glia* is derived from the Greek word for "glue," which gives you some idea of how the role of glial cells has been viewed in the past. However, glial cells do much more than hold neurons together. One of their most important functions is to increase the speed of conduction in neurons.

MYELINATION AND CONDUCTION SPEED

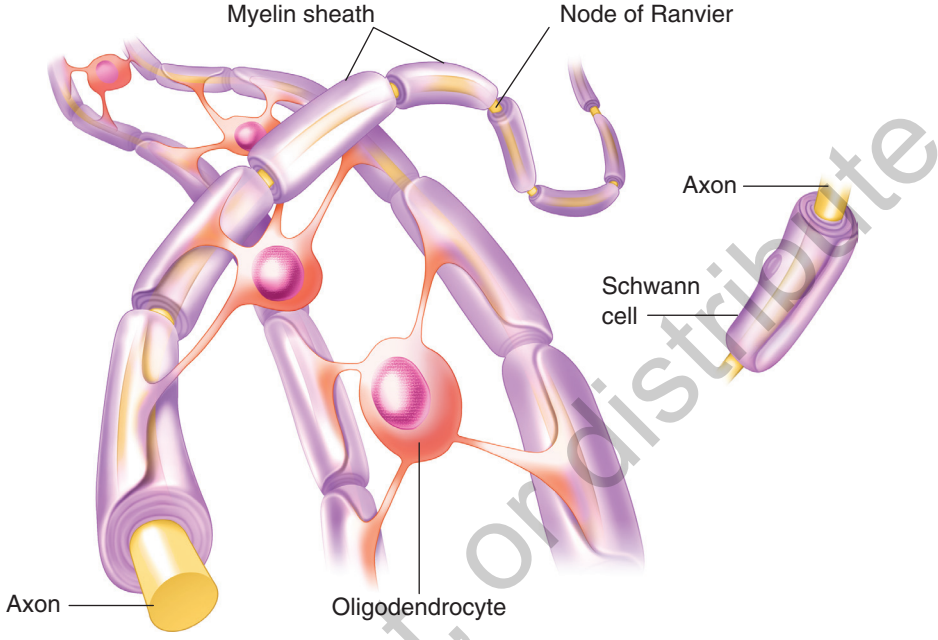
Survival depends in part on how rapidly messages can move through the nervous system, enabling the organism to pounce on its prey, outrun a predator, or process language quickly. The speed with which the fastest neurons conduct their impulses approaches 120 meters (m) per second (s), or about 270 miles per hour (435 km/hr). This seems fast, but the speed of electricity flowing through a wire, the analogy sometimes used to describe neural conduction, is up to 690 times faster. Because conduction speed is so critical to survival, strategies have evolved for increasing it. One way is to develop larger-diameter axons, which provide less resistance to the flow of electrical potentials. By evolving motor neurons with 0.5-mm-thick axons, the squid has achieved conduction speeds of 30 m/s, compared with 1 m/s in the smallest neurons.

? What are the functions of glial cells?

However, conduction speed increases not in direct proportion to axon size but closer to the square of the diameter (W. A. H. Rushton, 1951). To reach our four-times-greater maximum conduction speed of 120 m/s, our axons would have to be $4^2 = 16$ times larger than the squid axon, or 8 mm in diameter (the size of a large pea)! Obviously, your brain would be larger than you could carry around. In other words, if axon size were the only way to achieve fast conduction speed, *you* would not exist. Vertebrates (animals with backbones) have developed another solution, myelination. Two types of glial cells produce *myelin*, a fatty tissue that wraps around the axon (like a jellyroll) to insulate it from the surrounding fluid and from other neurons. Only the axon is covered, not the cell body. Myelin is produced in the brain and spinal cord by glial cells called *oligodendrocytes* and in the rest of the nervous system by

FIGURE 2.9 Oligodendrocytes Produce Myelin for Axons.

A single oligodendrocyte provides myelin for multiple segments of the axon and for multiple neurons. A Schwann cell covers only one segment of an axon.



Schwann cells (Figure 2.9). Almost 75% of the glial cells in the brain are myelin-producing oligodendrocytes (Pillay & Manger, 2007).

Because there are very few sodium channels under the myelin sheath, action potentials cannot occur there; conduction under myelinated areas is by local graded potential (Waxman & Ritchie, 1985). However, myelin appears in segments about 1 mm long, with a gap of one or two thousandths of a millimeter between segments; these gaps in the myelin sheath are called *nodes of Ranvier* (see Figure 2.9). At each node of Ranvier, where the membrane is exposed and there are plenty of sodium channels, the graded potential triggers an action potential. Action potentials thus appear to jump from node to node in a form of transmission called *saltatory conduction*.

This arrangement has three benefits. First, the insulating effect of myelin reduces an electrical effect of the membrane called capacitance. Because capacitance slows the movement of ions down the axon, the graded potential gets a big boost in speed. The overall effect of myelination is the equivalent of increasing the axon diameter 100 times (Koester & Siegelbaum, 2013). Second, the breaks in the myelination mean that the signal is regenerated by an action potential at every node of Ranvier. Third, myelinated neurons use much less energy because there is less work for the sodium-potassium pump to do.

Some diseases, such as multiple sclerosis, destroy myelin. As myelin is lost, the capacitance rises, reducing the distance that graded potentials can travel before dying out. The individual is worse off than if the neurons had never been myelinated; because there are few voltage-sensitive sodium channels under the myelin sheath (Ritchie & Rogart, 1977), action potentials may not be generated in the previously myelinated area. Therefore, conduction slows or stops in affected neurons.

OTHER GLIAL FUNCTIONS

There are several types of glial cells, and they make numerous contributions to neural functioning. During fetal development, *radial glia* form scaffolds that guide new neurons to their

FIGURE 2.10 Glial Cells Increase the Number of Connections Between Neurons.

Neurons were cultured for 5 days in (a) the absence of glial cells and (b) the presence of glia. The number of neurons was similar in both cultures; the greater density on the right is due to increased connections among both neurons.

Source: From F. W. Pfrieger and B. A. Barres, "Synaptic Efficacy Enhanced by Glial Cells In Vitro," *Science*, Vol. 277, p. 1684, 1997. Reprinted with permission from AAAS.

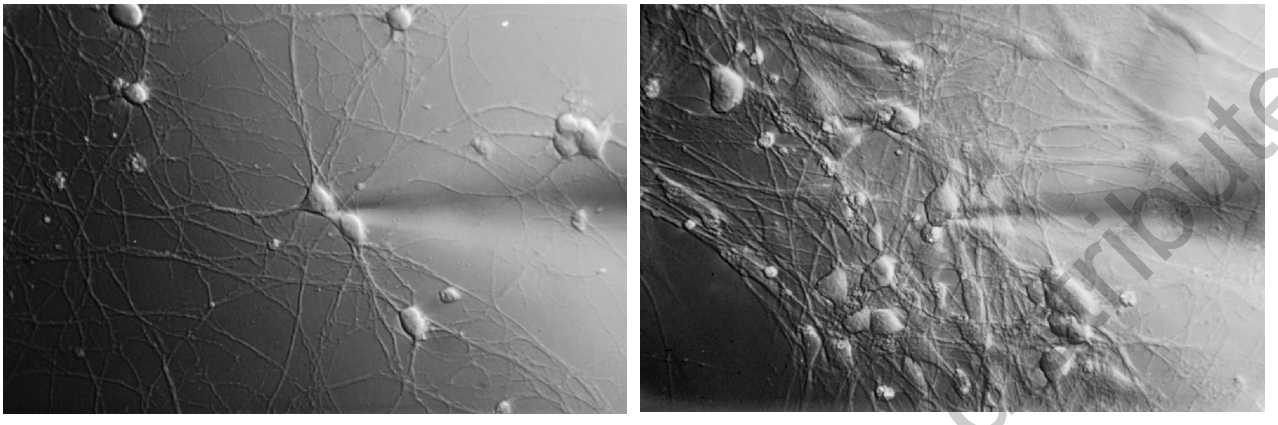
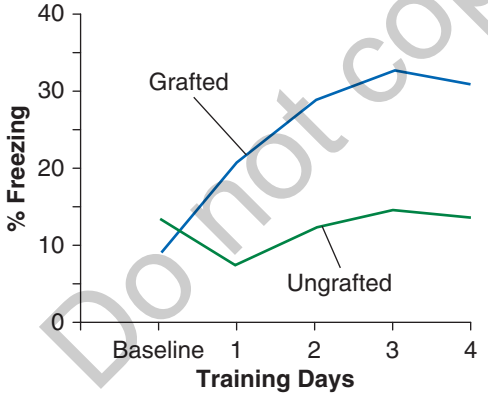


FIGURE 2.11 Human Glial Cells Enhance Conditioning in Mice.

Mice receiving brain grafts of human glial cells rapidly learned a fear response ("freezing" to a tone that signaled an upcoming electric shock), while ungrafted controls showed little or no improvement.

Source: Adapted from Figure 6B of "Forebrain Engraftment by Human Glial Progenitor Cells Enhances Synaptic Plasticity and Learning in Adult Mice," by Xiaoning Han et al., 2013, *Cell Stem Cell*, 12, p. 350.



destinations. Later on, *microglia* provide energy to neurons and respond to injury and disease by removing cellular debris. Neurons form seven times as many connections in the presence of the type of glia called *astrocytes*, and they start to lose their synapses if astrocytes are removed from the culture dish (Pfrieger & Barres, 1997; Ullian, Sapperstein, Christopherson, & Barres, 2001; see Figure 2.10). Astrocytes also appear to play a key role in learning, as Figure 2.11 demonstrates (X. Han et al., 2013; Suzuki et al., 2011). Later in this chapter, you will see that glial cells play a direct role in neural activity.

CONCEPT CHECK

Take a Minute to Check Your Knowledge and Understanding

- How is information conducted in the axon?
- How does the all-or-none law limit information transmission?
- What benefits do the refractory periods provide?
- How does myelin speed up conduction in axons?

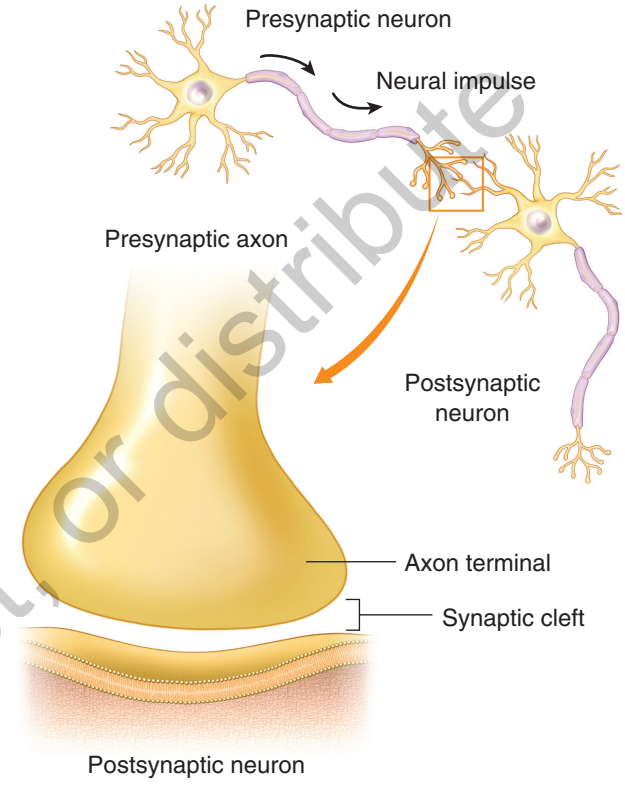
How Neurons Communicate With Each Other

Before the late 1800s, microscopic examination suggested that the brain consisted of a continuous web called a reticulum. At that point, however, Camillo Golgi developed a new tissue-staining method that helped anatomists see individual neurons by randomly staining some entire cells without staining others (see the discussion of staining methods in Chapter 4).

With this technique, the Spanish anatomist Santiago Ramón y Cajal (1937/1989) was able to see that each neuron is a separate cell. (See the For Further Reading section at the end of this chapter for more information about Ramón y Cajal's seminal work on describing the nervous system.) The connection between two neurons is called a *synapse*, a term derived from the Latin word that means "to grasp." The neurons are not in direct physical contact at the synapse but are separated by a small gap called the *synaptic cleft*. Two terms will be useful to us in the following discussion: The neuron that is transmitting to another is called the *presynaptic* neuron; the receiving neuron is the *postsynaptic* neuron (Figure 2.12).

FIGURE 2.12 The Synapse Between a Presynaptic Neuron and a Postsynaptic Neuron.

Notice the separation between the presynaptic axon terminal and the postsynaptic neuron.



Chemical Transmission at the Synapse

Until the 1920s, physiologists weren't sure whether neurons communicated at the synapse by an electrical current or by releasing a chemical. The German physiologist Otto Loewi believed that synaptic transmission was chemical, but he did not know how to test his hypothesis. One night, Loewi awoke from sleep with the solution to his problem (Loewi, 1953). He wrote his idea down so that he would not forget it, but the next morning, he could not read his own writing. He recalled that day as the most "desperate of my whole scientific life" (p. 33). But the following night, he awoke again with the same idea; taking no chances, he rushed to his laboratory. There he dissected out the beating hearts of two frogs and bathed them in a salt solution. He applied electrical stimulation to the vagus nerve attached to one of the hearts, which slowed the heartbeat. Then he extracted some of the salt solution, which he assumed would have captured any chemical that might have been released. When he applied this salt solution to the second heart, that heart slowed, too, just as Loewi predicted. Then he stimulated the accelerator nerve of the first heart, which caused the heart to beat faster. When he transferred the solution from the first heart to the second, this time it sped up (Figure 2.13). So Loewi demonstrated for the first time that transmission at the synapse is chemical and that neurons release at least two different chemicals with opposite effects.

? How does synaptic transmission differ from transmission in the axon?

It turned out later that some neurons do communicate electrically by passing ions through channels that connect one neuron to the next; their main function appears to be synchronizing activity in nearby neurons (M. V. L. Bennett & Zukin, 2004). In addition, some neurons release a gas transmitter. Still, Loewi was essentially correct because the majority of synapses are chemical. (By the way, if this example suggests to you that the best way to solve a problem is to "sleep on it," keep in mind that such insight occurs only when people have paid their dues in hard work beforehand!)

At chemical synapses, neurotransmitters are stored in the terminals in membrane-enclosed bubbles called *vesicles*; the term means, appropriately, "little bladders." When the action potential arrives at the terminals, it opens channels that allow calcium ions to enter the terminals from the extracellular fluid. The calcium ions cause the vesicles clustered nearest the membrane to fuse with the membrane. The membrane opens there, and the transmitter spills out and diffuses into the cleft in a process called *exocytosis* (Figure 2.14).

FIGURE 2.13 Loewi's Experiment Demonstrating Chemical Transmission in Neurons.

Loewi stimulated the first frog heart. When he transferred fluid from it to the second heart, it produced the same effect there as the stimulation did in the first heart.

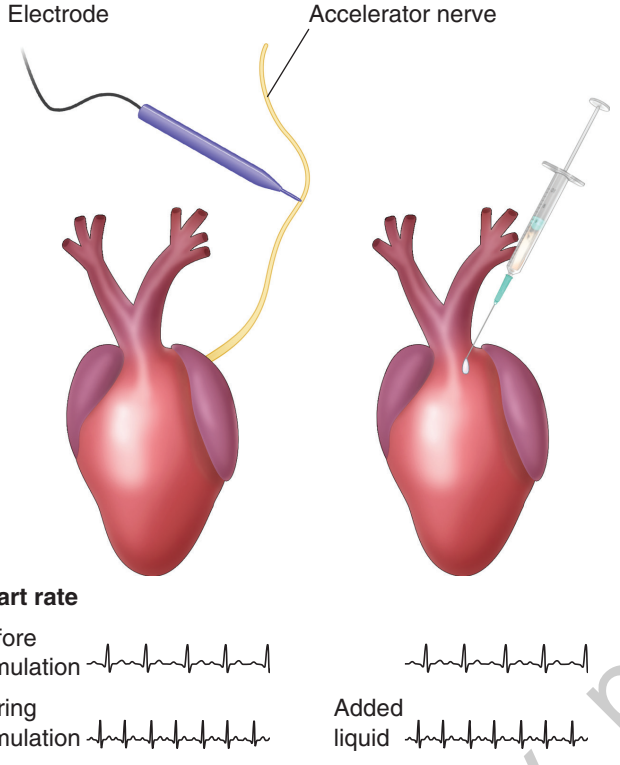
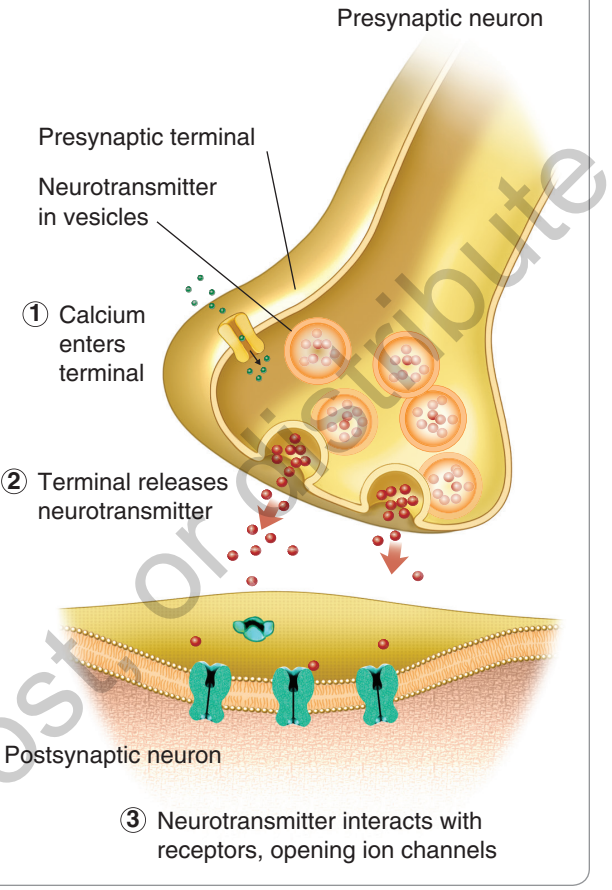


FIGURE 2.14 A Presynaptic Terminal Releases the Neurotransmitter at the Synapse.



On the postsynaptic neuron, the neurotransmitter docks with specialized protein receptors that match the molecular shape of the transmitter molecules like a key in a lock (see Figure 2.14). Activation of these receptors opens the ion channels, allowing ions to flow across the membrane. *Ionotropic receptors* form the ion channel and open quickly to produce the immediate reactions required for muscle activity and sensory processing. *Metabotropic receptors* open channels indirectly through a second messenger; they act slowly and produce longer-lasting effects. Opening the channels is what sets off the graded potential that initiates the action potential. You will see in the next section that the effect this has on the postsynaptic neuron depends on which receptors are activated.

The chemical jump across the synapse takes a couple of milliseconds; that is a significant slowing compared with transmission down the axon. In a system that places a premium on speed, inserting gaps in the neural pathway that slow down transmission must have some compensating benefit. As you will see in the following sections, synapses add important complexity to the simple all-or-none response in the axon.

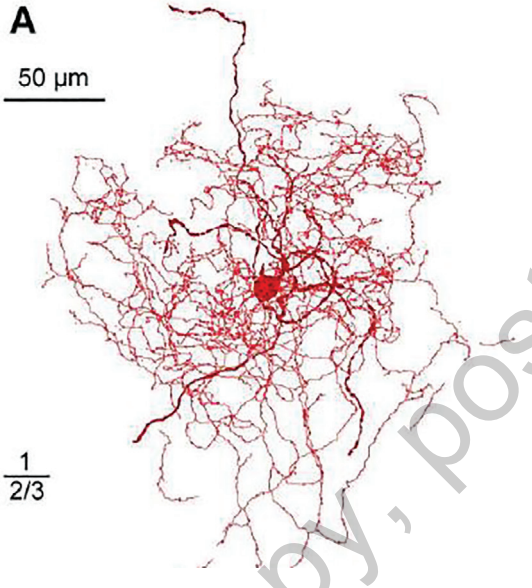
EXCITATION AND INHIBITION

Opening ion channels on the dendrites and cell body has one of two effects: It can cause the local membrane potential to shift in a positive direction toward zero, partially depolarizing the membrane, or it can shift the potential farther in the negative direction. *Partial depolarization* is excitatory and facilitates the occurrence of an action potential; increased polarization, or *hyperpolarization*, is inhibitory and makes an action potential less likely to occur. The value of excitation is obvious, but inhibition can communicate just as much information as excitation does.

Also, the message becomes more complex because input from one source can partially or completely negate input from another. In addition, inhibition helps prevent runaway excitation; one cause of the uncontrolled neural storms that sweep across the brain during an epileptic seizure is a deficiency in receptors for the inhibitory transmitter GABA (Baulac et al., 2001). Lithium, which is used to reduce manic symptoms of bipolar disorder, decreases excitatory neurotransmitters while increasing GABA transmission (Malhi, Tanious, Das, Coulston, & Berk, 2013). A Further Look describes an intriguing new finding about the importance of inhibition.

A FURTHER LOOK

A Neuron Type Found Only in Humans



A rosehip neuron in Layer 1 of the human cortex.

Source: Boldog, E., Bakken, T. E., Hodge, R. D., Novotny, M., Aevermann, B. D. et al. (2018). Transcriptomic and morphophysiological evidence for a specialized human cortical GABAergic cell type. Nature Neuroscience, 21, 1185–1195. Reprinted with permission.

In 2018, two teams of researchers collaborated to publish a description of a new neuron type that so far has been found only in humans (Boldog et al., 2018). It is a very small, compact neuron, with a bushy set of dendrites; the term *rosehip* was chosen because its appearance resembles a rose after it has lost its petals. Found in the outermost layer of the cortex (Layer 1), the neurons connect with a type of neuron in Layer 3 called pyramidal cells because of the conical shape of their cell body. When human pyramidal neurons fire, they also send excitatory output from their dendrites. The rosehip neurons appear to be exclusively inhibitory, and they produce dense synaptic connections on the pyramidal cell dendrites; the researchers suggest that the rosehip neurons' role may be to regulate this dendritic excitation.

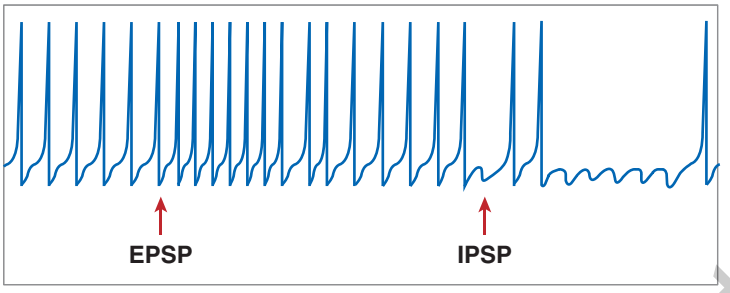
When the research teams looked for rosehip neurons in rodents, they could not find them, which may make them one of the very few uniquely human aspects of the nervous system. Interestingly, pyramidal cells in mice lack the excitatory "backpropagation" that characterizes human pyramidal cells, which may explain why humans have rosehip neurons and mice apparently do not. The researchers also found patterns of gene expression in the rosehip neurons that have been implicated in neuropsychiatric disease, so one of their next steps is to see if the neurons are involved in these disorders (Servick, 2018).

What determines whether the effect on the postsynaptic neuron is exciting or inhibiting? It depends on a combination of which transmitter is released and the type of receptors on the postsynaptic neuron. A particular transmitter can have an excitatory effect at one location in the nervous system and an inhibitory effect at another; however, some transmitters typically produce excitation, and others most often produce inhibition. If the receptors open sodium channels, this produces a partial depolarization of the dendrites and cell body, which acts as an *excitatory postsynaptic potential (EPSP)*. Other receptors open potassium channels, chloride channels, or both; as potassium moves out of the cell or chloride moves in, it produces a hyperpolarization of the dendrites and cell body, or an *inhibitory postsynaptic potential (IPSP)*.

At this point, there is only a graded local potential. This potential spreads down the dendrites and across the cell body to the *axon hillock* (where the axon joins the cell body). Here,

FIGURE 2.15 Effect of Excitation and Inhibition on Spontaneous Firing Rate.

Source: Adapted from *Principles of Neural Science*, 5th ed., by E. R. Kandel et al., p. 213. © 2013, McGraw-Hill Companies, Inc.



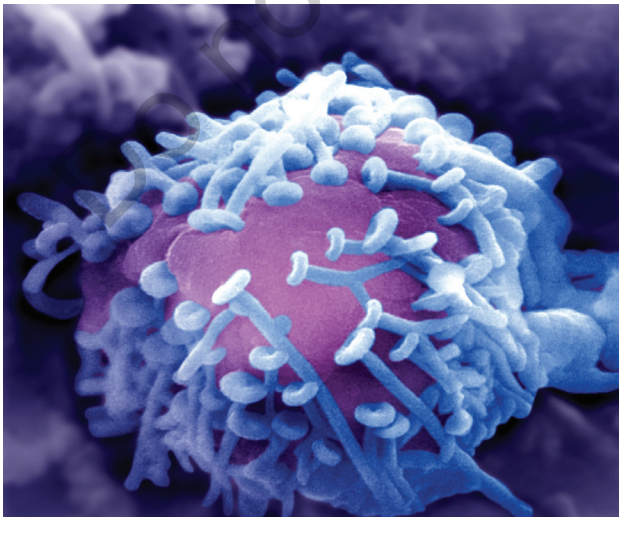
a positive graded potential that surpasses threshold will produce an action potential; a negative graded potential will make it less likely to be generated. Most neurons have a baseline rate of spontaneous action potential generation; EPSPs will increase this rate, while IPSPs will decrease the rate of firing (Figure 2.15). So now another form of complexity has been added at the synapse: The message to the postsynaptic neuron can *modulate* the rate of firing, not just turn it on or off.

You should not assume that excitation of neurons always corresponds to activation of behavior or that inhibition necessarily suppresses behavior. An EPSP may activate a neuron that has an inhibitory effect on other neurons, and an IPSP may reduce activity in a neuron that has an inhibitory effect on other neurons, increasing their activity. An example of this paradox at the behavioral level is the effect of Ritalin. Ritalin and many other medications used to treat attention-deficit/hyperactivity disorder (ADHD) in children are in a class of drugs called stimulants, which increase activity in the nervous system. Yet in low doses, they calm hyperactive individuals and improve their ability to concentrate and focus attention (D. J. Cox, Merkel, Kovatchev, & Seward, 2000; Mattay et al., 1996). They do this by increasing stimulating neurotransmitters in frontal areas of the brain that normally restrain behavior, where activity has been found to be abnormally low in people with ADHD (Berridge et al., 2006; Faigel, Szuajderman, Tishby, Turel, & Pinus, 1995).

? What are summation and integration?

Next, you will see that the ability to combine the inputs of large numbers of neurons expands the synapse's contribution to complexity even further.

FIGURE 2.16 A Cell Body Virtually Covered With Axon Terminals.



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POSTSYNAPTIC INTEGRATION

The output of a single neuron is not enough by itself to cause a postsynaptic neuron to fire or to prevent it from firing. In fact, an excitatory neuron may depolarize the membrane of the postsynaptic neuron by as little as 0.2 to 0.4 mV (Siegelbaum, Kandel, and Yuste, 2013); remember that it takes an approximately 10-mV depolarization to trigger an action potential. However, a typical neuron receives input from approximately 1,000 other neurons (Figure 2.16); because each neuron has numerous terminals, this amounts to as many as 10,000 synaptic connections in most parts of the brain and up to 100,000 in the cerebellum (Siegelbaum & Kandel, 2013).

Because a single neuron has a relatively small effect, the postsynaptic neuron must combine potentials from many neurons to fire. This requirement is actually advantageous: It ensures that a neuron will not be fired by the spontaneous activity of a single presynaptic neuron, and it allows the neuron to combine multiple inputs into a more complex

message. These potentials are combined at the axon hillock in two ways. *Spatial summation* combines potentials occurring simultaneously at different locations on the dendrites and cell body. *Temporal summation* combines potentials arriving a short time apart, from either the same or separate inputs. Temporal summation is possible because a local potential persists for a few milliseconds. Spatial summation and temporal summation occur differently, but they have the same result. Summation is illustrated in Figure 2.17.

As you can see in Figure 2.18, summation combines EPSPs so that an action potential is more likely to occur. Alternatively, summation of IPSPs drives the membrane's interior even more negative and makes it more difficult for incoming EPSPs to trigger an action potential. When both excitatory and inhibitory impulses arrive on a neuron, they will summate algebraically. The combined effect will equal the difference between the sum of the partial depolarizations and the sum of the hyperpolarizations. Spatial summation of two excitatory inputs and one inhibitory input is illustrated in Figure 2.19. The effect from temporal summation would be similar.

Because the neuron can summate inputs from multiple sources, it rises above the role of a simple message conductor—it is an *information integrator*. And using that information, it functions as a *decision maker*, determining whether to fire or not. Thus, the nervous system becomes less like a bunch of electrical wires and more

FIGURE 2.17 Spatial and Temporal Summation.

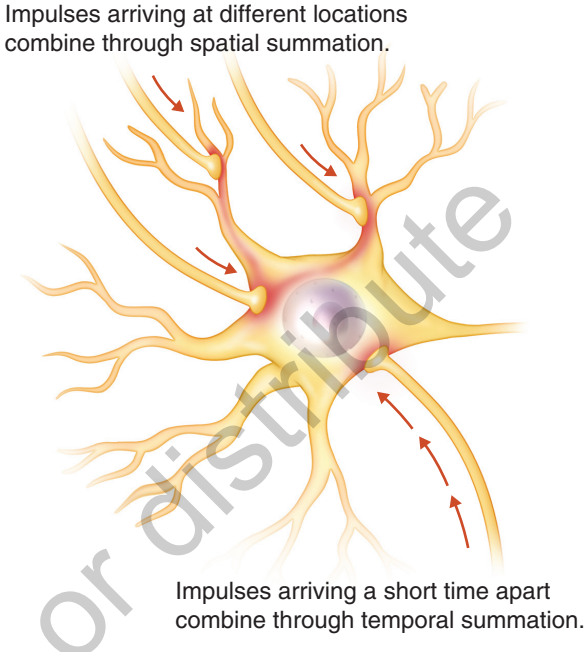


FIGURE 2.18 Temporal and Spatial Summation.

An EPSP (Point 1); temporal summation of two EPSPs (2); temporal summation of three EPSPs reaches threshold (3); spatial summation of EPSPs reaches threshold (4); an IPSP (5); temporal summation of two IPSPs (6).

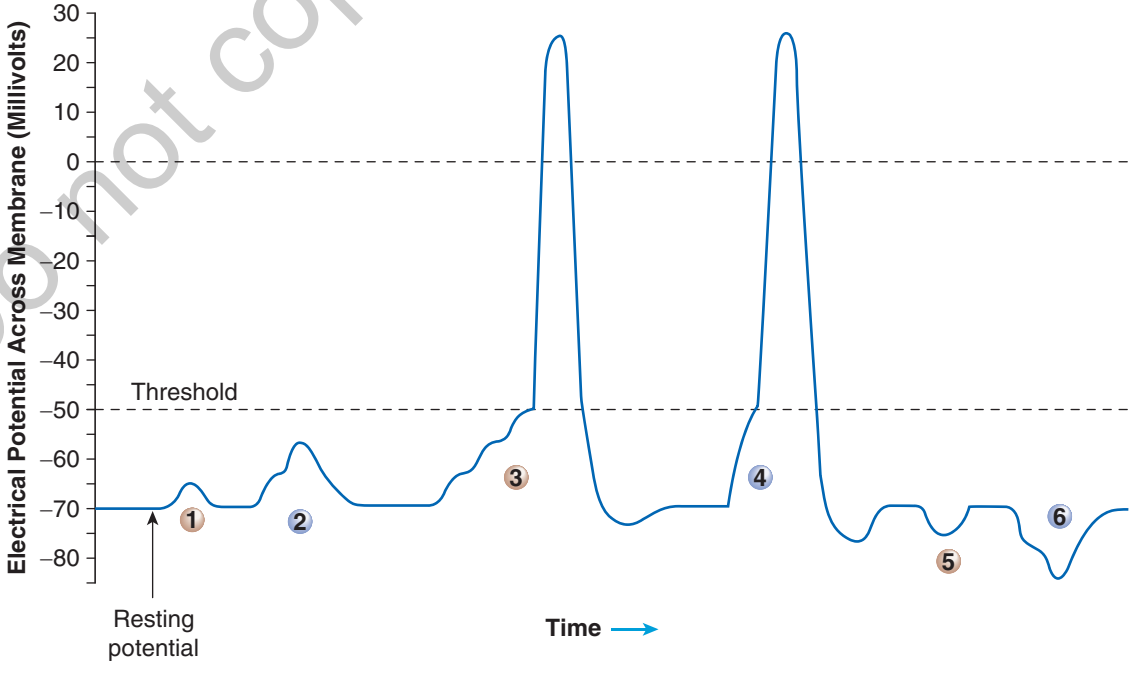
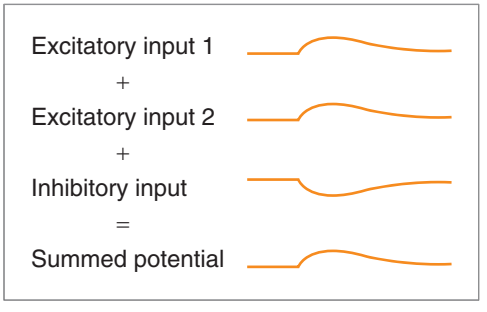


FIGURE 2.19 Spatial Summation of Excitatory and Inhibitory Potentials.

Note that inhibitory potentials cancel out excitatory potentials of equal strength (and vice versa).



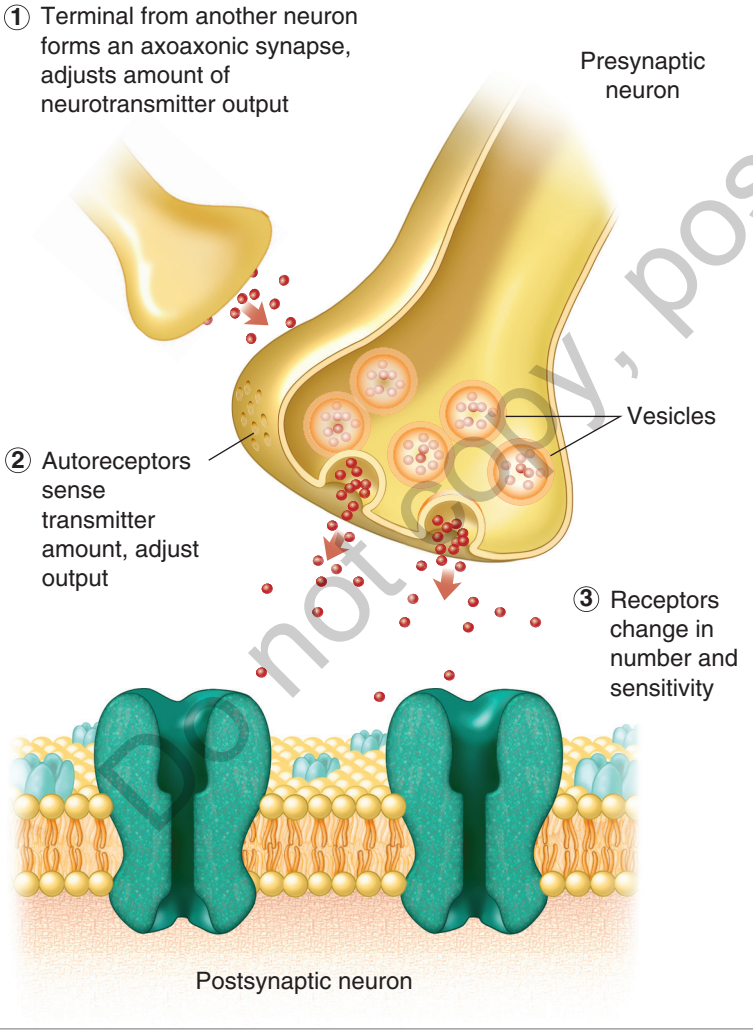
like a computer. In subsequent chapters, you will come to appreciate how important the synapse is in understanding how we see, how we learn, and how we succumb to mental illness.

TERMINATING SYNAPTIC ACTIVITY

Usually, the transmitter must be inactivated; otherwise, it will continue to stimulate postsynaptic receptors or leak over to other synapses and interfere with their functions. Typically, transmitters are taken back into the terminals by membrane proteins called transporters in a process called *reuptake*; they are repackaged in vesicles to be used again. At some synapses, the transmitter in the cleft is absorbed by nearby astrocytes. In others, transmitters are partially broken down through a process called inactivation. The neurotransmitter acetylcholine, for example, is inactivated by the enzyme acetylcholinesterase, which splits the molecule into its components of choline and acetate. Choline is then taken back into the terminals and used to make more acetylcholine.

Controlling how much neurotransmitter remains in the synapse is one way to vary behavior, and many drugs capitalize on this mechanism. Cocaine blocks the reuptake of dopamine; some antidepressant medications block the reuptake of serotonin, norepinephrine, or both, whereas others (*MAO inhibitors*) prevent the enzyme monoamine oxidase from inactivating those transmitters as well as dopamine and epinephrine; and drugs for treating the muscular disorder myasthenia gravis increase acetylcholine availability by inhibiting the action of acetylcholinesterase.

FIGURE 2.20 Regulating Activity at the Synapse.



Regulating Synaptic Activity

The previous description has been of a linear system that amounts to *"neuron A stimulates neuron B, neuron B stimulates neuron C,"* and so on. However, such a simple system cannot transmit the complex information required to solve a math equation, write a symphony, or care for a newborn. Not only that, but as messages flow from neuron to neuron, activity would soon drift out of control; some activity would fade out, while other activity would escalate until it engulfed an entire area of the brain. A nervous system that controls complex behavior must have several ways to regulate its activity.

The synapses described so far are referred to as *axodendritic* and *axosomatic* synapses, because their terminals connect to dendrites and cell bodies. At *axoaxonic* synapses, a third neuron releases transmitter onto the terminals of the presynaptic neuron (see Point 1 in Figure 2.20). The result is *presynaptic excitation* or *presynaptic inhibition*, which

increases or decreases, respectively, the presynaptic neuron's release of neurotransmitter onto the postsynaptic neuron. One way an axoaxonic synapse can adjust a presynaptic terminal's activity is by regulating the amount of calcium entering the terminal, which, you will remember, triggers neurotransmitter release.

Neurons also regulate their own synaptic activity in two ways. *Autoreceptors* on the presynaptic terminals sense the amount of transmitter in the cleft; if the amount is excessive, the presynaptic neuron reduces its output (Figure 2.20, Point 2). Postsynaptic neurons participate in regulation of synaptic activity as well. When there are unusual increases or decreases in neurotransmitter release, postsynaptic receptors change their sensitivity or even their numbers to compensate (Figure 2.20, Point 3). You will find in Chapter 14 that receptor changes figure prominently in some psychological disorders, such as schizophrenia.

? What are the three ways of regulating synaptic activity?

Glial cells also contribute to the regulation of synaptic activity. They surround the synapse and prevent neurotransmitter from spreading to other synapses, but some also remove neurotransmitter from the synaptic cleft and recycle it for the neuron's reuse (Figure 2.21). By varying the amount of transmitter they remove, glial cells influence postsynaptic excitability (Oliet, Piet, & Poulain, 2001). They can even respond to the neurotransmitter level in the synapse by releasing transmitters of their own. These gliotransmitters regulate transmitter release from the presynaptic neuron or directly stimulate the postsynaptic neuron to excite or inhibit it (M. Anderson & Hanse, 2010; Newman, 2003). Thus, rather than simply being neural "glue" as the name implies, glia should be considered active partners in neural transmission.

Neurotransmitters

Table 2.2 on page 40 lists twelve transmitters, grouped according to their chemical structure. This is an abbreviated list; there are other known or suspected transmitters, and there are doubtless additional transmitters yet to be discovered. This summary is intended to illustrate

FIGURE 2.21 Glial Cell Interacting With Neurons at the Synapse.

An astrocyte, a type of glial cell, encloses the synapse, where it absorbs the neurotransmitter glutamate (Glu) from the synaptic cleft. It recycles the transmitter into its precursor glutamine (Gln) and returns the Gln to the presynaptic terminal for reuse. The glial cell can influence synaptic activity by granting or withholding transmitter absorption and by releasing its own transmitter in response to the neurotransmitter level in the synapse.

Source: Adapted with permission from "Energy on Demand," by P. J. Magistretti et al., 1999, *Science*, 283, p. 497. Copyright © 1999. Reprinted with permission from AAAS.

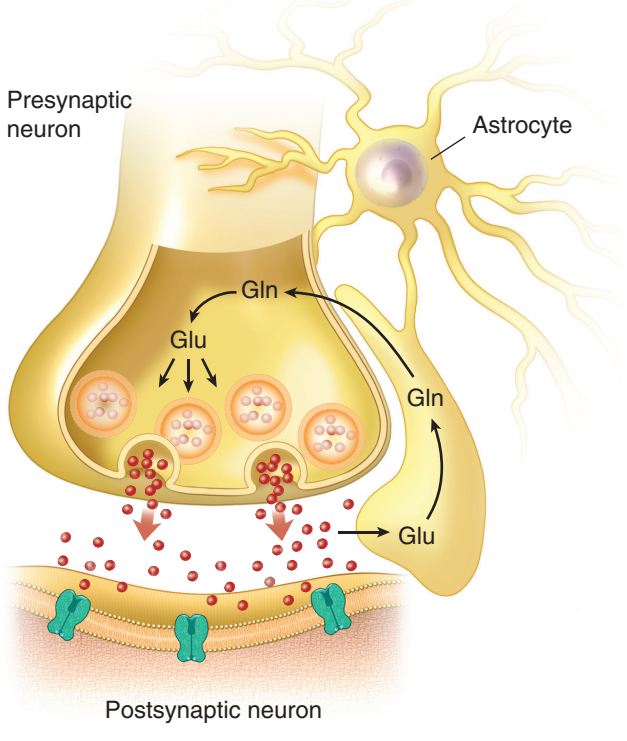


TABLE 2.2 Some Representative Neurotransmitters.

NEUROTRANSMITTER	FUNCTION
Acetylcholine	Transmitter at muscles; in brain, involved in learning, etc.
Monoamines	
Serotonin	Involved in mood, sleep and arousal, aggression, depression, obsessive-compulsive disorder, and alcoholism.
Dopamine	Contributes to movement control and promotes reinforcing effects of food, sex, and abused drugs. Dysregulation is involved in schizophrenia and Parkinson's disease.
Norepinephrine	A hormone released during stress. Functions as a neurotransmitter in the brain to increase arousal and attentiveness to events in the environment. Diminished norepinephrine transmission is involved in depression.
Epinephrine	A stress hormone related to norepinephrine; plays a minor role as a neurotransmitter in the brain.
Amino Acids	
Glutamate	The principal excitatory neurotransmitter in the brain and spinal cord. Vitally involved in learning; glutamate dysfunction is implicated in schizophrenia.
Gamma-aminobutyric acid (GABA)	The predominant inhibitory neurotransmitter. Its receptors respond to alcohol and the class of tranquilizers called benzodiazepines. Deficiency in GABA or receptors is one cause of epilepsy.
Glycine	Inhibitory transmitter in the spinal cord and lower brain. The poison strychnine causes convulsions and death by affecting glycine activity.
Neuropeptides	
Endorphins	Neuromodulators that reduce pain and enhance reinforcement.
Substance P	Transmitter in neurons sensitive to pain.
Neuropeptide Y	Initiates eating and produces metabolic shifts.
Gas	
Nitric oxide	One of two known gaseous transmitters, along with carbon monoxide. Can serve as a retrograde transmitter, influencing the presynaptic neuron's release of neurotransmitter. Viagra enhances male erections by increasing nitric oxide's ability to relax blood vessels and produce penile engorgement.

the variety in neurotransmitters and to give you some familiarity with the functions of a few of the major ones. You will encounter most of them again in the discussion of various behaviors in later chapters.

Having a variety of neurotransmitters multiplies the effects that can be produced at synapses; the fact that there are different subtypes of the receptors adds even more. For example, two types of receptors detect acetylcholine: the nicotinic receptor, so called because it is also activated by nicotine, and the muscarinic receptor, named for the mushroom derivative that can stimulate it. Nicotinic receptors are excitatory; they are found in muscles and, in lesser numbers, in the brain. Muscarinic receptors are more frequent in the brain, where they have an excitatory effect at some locations and an inhibitory one at others. Other transmitters have many more receptor subtypes than acetylcholine does.

For decades, neurophysiologists labored under the erroneous belief, known as *Dale's principle*, that a neuron was capable of releasing only a single transmitter. We now know that many neurons ply their postsynaptic partners with more than one chemical messenger

(Vaaga, Borisovska, & Westbrook, 2014). These neurons may release two fast-acting neurotransmitters, a fast-acting neurotransmitter and a slow-acting monoamine, or a fast-acting neurotransmitter and a neuromodulator, which alters the effect of the transmitter. There is even evidence that some neurons release more than two neurotransmitters, for example, dopamine, gamma-aminobutyric acid (GABA), and glutamate. And some neurons can release one transmitter in response to weak stimulation and another during strong stimulation. As you can now see, chemical transmission vastly increases the complexity of the nervous system.

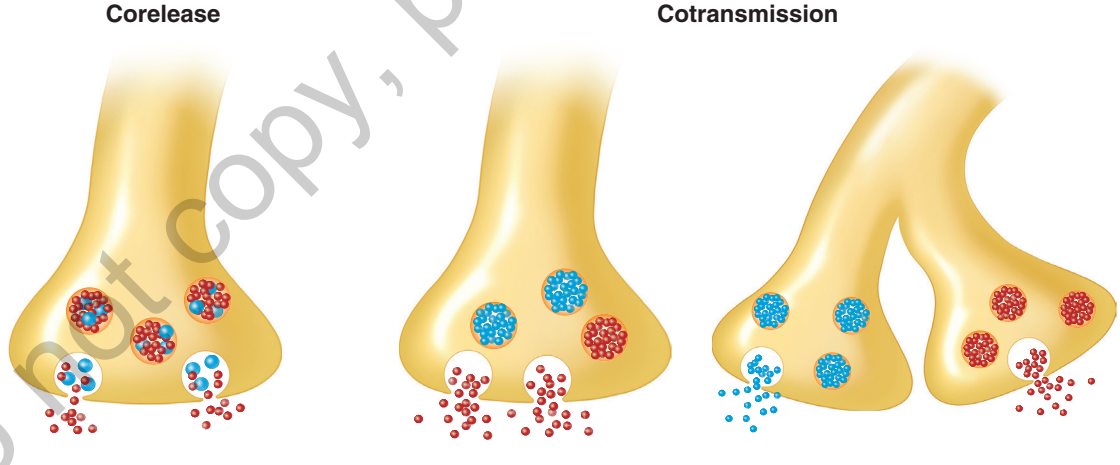
? What are two additional ways synapses add information complexity?

The release can occur in three ways. In *corelease*, the transmitters are packaged in the same vesicles. However, this doesn't mean they're always released equally; in the example in Figure 2.22a, the fusion pores between the vesicle and terminal membranes have opened only partially, impeding the release of the larger messenger molecules while allowing the smaller molecules to exit freely (see M. Braun et al., 2007). In *cotransmission*, the transmitters are in separate vesicles. Vesicles containing different transmitters in the same terminal differ in sensitivity to calcium (Ca^{2+}); a low rate of neural impulses will trigger release of only one of the messengers, whereas a higher rate will release both of them (Figure 2.22b). Finally, the neuron may release different transmitters from its various terminals to produce different effects at separate destinations (Figure 2.22c).

FIGURE 2.22 Neural Corelease and Cotransmission.

(a) In corelease, the neuron can limit exit of larger chemical messengers by partially opening the fusion pore. (b) When the messengers are in different vesicles in the same terminal, the vesicles' differential Ca^{2+} sensitivity provides release selectivity. (c) Packaging the transmitters in separate terminals allows the neuron to have different effects at the terminals' destinations.

Source: Adapted from "Dual-transmitter Neurons: Functional Implications of Co-release and Co-transmission," by C. E. Vaaga, M. Borisovska, and G. L. Westbrook, 2014, *Current Opinions in Neurobiology*, 29, 25–32.



Corelease and cotransmission are not well understood, but we do know they play a significant role in neural functioning. For example, release of inhibitory GABA dampens the excitatory effects of glutamate during seizures (Trudeau, 2004) and counters the arousing effects of histamine to prevent hyperactivity and sustained wakefulness (Yu et al., 2015). In addition, direction-detecting cells in the retina of the eye release acetylcholine and GABA in response to any movement of a visual object, but they release only GABA when the movement is in the cell's "preferred" direction (S. Lee, Kim, & Zhou, 2010).

A FURTHER LOOK

Agonists and Antagonists in the Real World

Amazonians tip their blowgun darts with the plant neurotoxin curare.

Source: By Jialiang Gao, https://commons.wikimedia.org/wiki/File:Yahua_Blowgun_Amazon_Iquitos_Peru.jpg, licensed under CC BY-SA 4.0 https://creativecommons.org/licenses/by-sa/4.0/.

Neurotransmitters are not the only substances that affect the nervous system. The many drugs and other compounds that mimic or increase the effect of a neurotransmitter are called *agonists*. Any substance that reduces the effect of a neurotransmitter is called an *antagonist*. Practically all drugs that have a psychological effect interact with a neurotransmitter system in the brain, and many of them do so by mimicking or by blocking the effect of neurotransmitters (S. H. Snyder, 1984).

You have already seen that the effect of acetylcholine (ACh) is duplicated by nicotine and muscarine at the two kinds of acetylcholine receptors (nicotinic-ACh and muscarinic-ACh, respectively). Opioid drugs such as heroin and morphine also act as agonists, stimulating receptors for opiate-like transmitters in the body. The drugs naloxone and naltrexone act as antagonists to opiates, occupying the receptor sites without activating them; consequently, naloxone and naltrexone can be used to counteract an overdose. The plant toxin curare blocks nicotinic acetylcholine receptors at the muscle, causing paralysis (A. Trautmann, 1983). Indigenous tribes of Central and South America put curare on the tips of their darts and arrows to disable their game. A synthetic version of curare was used as a muscle relaxant during surgery before safer and more effective drugs were found (M. Goldberg & Rosenberg, 1987). It was even used occasionally in the past to treat the muscle spasms of tetanus (lockjaw), which, ironically, is caused by another neurotoxin.

Neural Codes and Neural Networks

Underlying this discussion has been the assumption that we can explain behavior by understanding what neurons do. But we cannot make good on that promise as long as we talk as if neural communication is limited to single chains of neurons that either fire or don't fire. In fact, neurons are capable of generating complex messages, which they send across intricate networks.

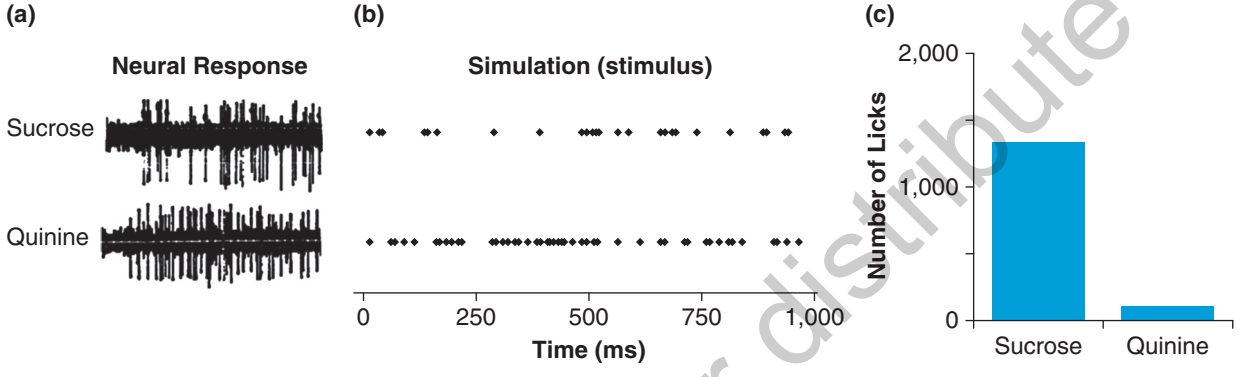
CODING OF NEURAL MESSAGES

Neurons don't just produce a train of equally spaced impulses: They vary the intervals between spikes, they produce bursts of varying lengths, and the bursts can be separated by different intervals (Cariani, 2004). But do these temporal (time-related) variations in firing pattern form a code that the brain can use, or are they just "noise" in the system? The best way to answer this question is to look at sensory processes, because the researcher can correlate firing patterns with sensory input on one end and behavior on the other. A good example is an early study done by Patricia Di Lorenzo and her colleague Gerald Hecht (1993). First, they recorded the firing patterns in individual taste neurons of rats during stimulation with a sucrose (sugar) solution and quinine (the flavoring in tonic water). As you can see in Figure 2.23a, these flavors produce different neural activity. Then they duplicated the temporal patterns in the form of electrical pulses (Figure 2.23b) and used these to stimulate the taste pathways of other rats. The assumption was that if the brain *uses* this information, the unanesthetized rats would behave as if they were actually *tasting* sweet

FIGURE 2.23 Response of Rats to Neural Stimulation Simulating the Taste of Sucrose and Quinine.

(a) Recordings from individual neurons during stimulation with sucrose and quinine. (b) Electrical stimulation mimicking the recorded neuronal activity: Each dot represents a signal neural impulse. (c) The average number of times the rats licked a drinking tube for water during delivery of the quinine simulation and the sucrose simulation.

Sources: (a) and (b) Adapted from Figure 7 of "Temporal Coding in the Gustatory System," by R. M. Hallock and P. M. Di Lorenzo, 2006, *Neuroscience and Biobehavioral Reviews*, 30, p. 1156. Used with permission from Elsevier. (c) Adapted from Figure 4 of "Perceptual Consequences of Electrical Stimulation in the Gustatory System," by P. M. Di Lorenzo and G. S. Hecht, 1993, *Behavioral Neuroscience*, 107, p. 135.



sucrose or bitter quinine. As Figure 2.23c shows, that is exactly what happened: The rats licked a water tube at a high rate when they were receiving stimulation patterned after sucrose but almost stopped licking—even though they were water deprived—when the stimulation was patterned after quinine.

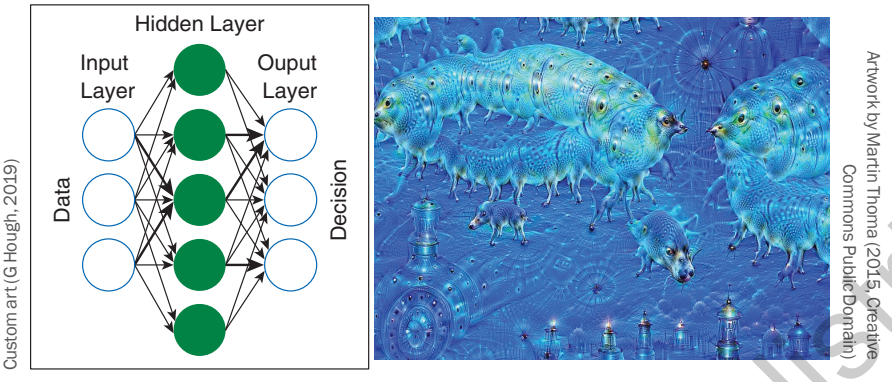
However, this coding apparently is not sufficient to carry the complex information involved in brain communication. An additional opportunity for coding is provided by the fact that neural information often travels over specialized pathways. For example, taste information is carried by at least five types of specialized fibers; Di Lorenzo and Hecht (1993) recorded the sucrose firing pattern from a "labeled line" specialized for sweet stimuli and the quinine pattern from another specialized for bitter stimuli. In later chapters, you will see that not only taste but also information about color and about the higher sound frequencies is transmitted over a limited number of labeled lines. However, even with temporal coding and labeled lines, a significant burden remains for the brain if it is to make sense of this information. This leads us to the topic of neural networks.

NEURAL NETWORKS

Individual neurons cannot carry enough information to determine the taste of a bite of food or the color of an object. Color processing, for example, depends on four "labeled lines" carrying information about red, green, blue, and yellow light; we can distinguish millions of colors by comparing the relative activity in these four pathways. This kind of analysis requires complex interactions among a network of neurons. *Neural networks* are groups of neurons that function together to carry out a process; they are where the most complex neural processing—the "computing" work of the brain—occurs. Sometimes these networks involve a relatively small number of neurons in a single area, such as groups of neurons in a part of the brain called the hippocampus. When rats navigate a maze, these networks store their preceding choices and calculate their next choice. The networks perform so reliably that the researcher can use their activity to predict which way the rat will turn after a delay (Pastalkova, Itskov, Amarasingham, & Buzsáki, 2008). As you will see in later chapters, other networks combine the activity of widespread brain areas to perform language functions (Chapter 9), to identify an object visually and locate it in space (Chapter 10), and, some researchers believe, to produce conscious awareness (Chapter 15). We go into more detail about other uses of neural networks, such as in the creation of art and in deceptive video editing, in A Further Look.

A FURTHER LOOK

Uses and Abuses of Artificial Neural Networks



Left: Example of a simple artificial neural network. Right: DeepDream image produced from a picture of jellyfish after 50 iterations, by a network trained on pictures of dogs.

Artificial neural networks are computer programs that mimic the brain's neural networks; rather than being programmed to perform in a specific way, these networks *learn* how to carry out their task by trial and error, much as we do. The networks consist of multiple layers of simulated neurons: an input layer, one or more hidden layers where the processing is done, and an output layer. The network is trained by repeatedly feeding it data, then giving it correct results to compare with its own output. At first, the network's performance is random, but it improves over time by adjusting the strength of connections among its simulated neurons. For example, an early network that was designed to read and speak English text initially produced random sounds, which were replaced with babbling and then pseudowords, but after just 10 training trials, the speech was intelligible and sounded like a small child's (Sejnowski & Rosenberg, 1987).

Artificial neural networks can be used to identify people through face recognition, control a self-driving car, or detect alterations to an image or video (Coldeway, 2019). They are especially useful in tasks requiring decision making, such as in finance, but also as far afield as in art. *DeepDream* software, which was created to recognize faces and other patterns in images, can be run in reverse to produce "psychedelic" and surreal art. The two photographs here were created from a picture of jellyfish by a network that was trained to perceive dogs, so it gave the jellyfish image "dog" characteristics.

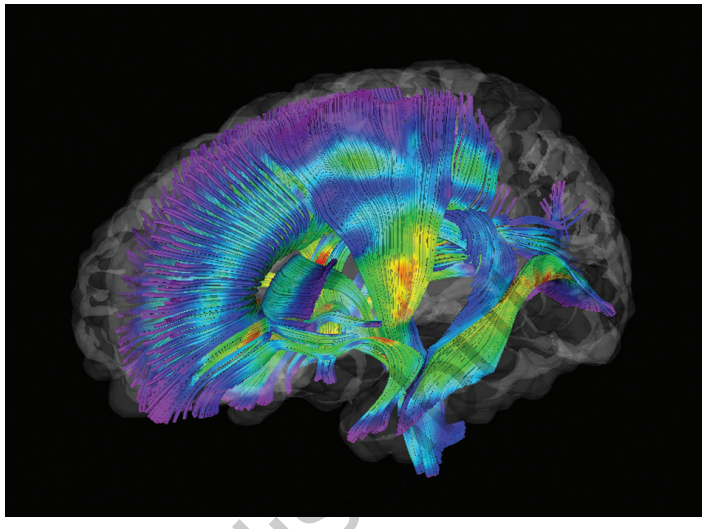
But anything this powerful is subject to abuse; a good example is *deepfake* videos. These originated as fake pornographic videos of celebrities, created by collecting multiple photos of the person from around the web and superimposing them on the body of an actor. More recently, a deepfake video appearing to show Facebook's Mark Zuckerberg saying he has "total control of billions of people's stolen data" went viral on the web. The frightening potential exists to create convincing fake evidence of a person committing a crime or a video of a political opponent making reprehensible statements. As a means of warning about the risks of such "fake news," director Jordan Peele and BuzzFeed CEO Jonay Peretti created a deepfake video of Barack Obama calling Trump a "complete and utter dips__t" (Chivers, 2019).

Understanding these networks is the next big frontier in brain research. Their complexity and relative inaccessibility are challenging researchers' resolve and ingenuity, but developments in brain-imaging capabilities make the goal more realistic. The *Human Connectome Project* is a large-scale, multi-university effort to map the brain's circuits. Its researchers are using a combination of four scanning techniques, behavioral measures, and genetic analysis to determine the brain's anatomical and functional connectivity (Van Essen et al., 2013). The

FIGURE 2.24 Image of White Matter Fiber Tracts.

This image is from the brain of an infant at risk for autism, based on having older siblings with autism. Those who were diagnosed with autism at 24 months had already begun to differ in tract development by the age of 6 months (Wolff et al., 2012). The study used a white matter imaging technique called diffusion tensor imaging; colors represent varying strengths of connection.

Source: Jason Wolff, PhD, University of North Carolina at Chapel Hill.



maps will help researchers understand normal brain functioning in realms such as learning and consciousness, as well as disorders in functioning, including autism and schizophrenia (Figure 2.24). By the way, it took more than a decade to map the roundworm's brain, with just 300 neurons and 7,000 connections, so attempting it for the human brain is a very tall order.

While we're waiting for neuroscientists to explain how the brain works, the idea of neural networks provides a useful way of thinking about mental processes. The next time you are trying to remember a person's name that is "on the tip of your tongue," imagine your brain activating individual components of a neural network until one produces the name you're looking for. If you visualize the person's face as a reminder, imagine that the name and the image of the face are stored in connected networks, so that activating one memory activates the other. This is not just speculation: Electrode recordings from patients preparing for brain surgery show that the information triggered by the photo of a familiar person and by the person's written name converge on the same neurons in a critical memory area of the brain (Quian Quiroga, Kraskov, Koch, & Fried, 2009)—thanks, of course, to neural networks.

CONCEPT CHECK

Take a Minute to Check Your Knowledge and Understanding

- How is information transmitted at the synapse?
- It can be said that integration transforms neurons from a "telephone line" into a computer. Explain.
- What difference would it make if there were no regulation of activity at the synapse?
- What is Dale's principle, and in what way is it incorrect?
- Explain why researchers' focus is shifting from localized neural activity to brainwide connections and activity.
- What are artificial neural networks?

In Perspective

It is impossible to understand either the brain or behavior without first knowing the capabilities and the limitations of the neuron. Although more complexity is added at the synapse,

a relatively simple device is the basis for our most sophisticated capabilities and behaviors. However, what happens at the individual neuron is not enough to account for human behavior; neurons work in concert with each other, in both local and brainwide networks. With modern tools and large cooperative efforts, researchers hope to understand how neurons work together to produce thought, memory, emotion, and consciousness. In Chapter 3, you will learn about some of the functional structures in the brain that are formed by the interconnection of neurons.

CHAPTER SUMMARY

THE CELLS THAT MAKE US WHO WE ARE

- There are three major kinds of neurons: motor neurons, sensory neurons, and interneurons. Although they play different roles, they have the same basic components and operate the same way.
- The neural membrane is electrically polarized. This polarity is the resting potential, which is maintained in the short term by the effects of selective membrane permeability in combination with the forces of diffusion and electrostatic pressure and in the long term by the sodium-potassium pump.
- Polarization is the basis for the neuron's responsiveness to stimulation, in the form of the graded potential and the action potential.
- The neuron is limited in firing rate by the absolute refractory period and in its ability to respond to differing strengths of stimuli by the all-or-none law. More intense stimuli cause the neuron to fire earlier during the relative refractory period, providing a way to encode stimulus intensity (the rate law).
- Glial cells provide the myelination that enables neurons to conduct rapidly while remaining small. They also help regulate activity in the neurons and provide several supporting functions for neurons.

HOW NEURONS COMMUNICATE WITH EACH OTHER

- Transmission from neuron to neuron is usually chemical in vertebrates, involving neurotransmitters released onto receptors on the postsynaptic dendrites and cell body.
- The neurotransmitter can create an excitatory postsynaptic potential, which increases the chance that the postsynaptic neuron will fire, or it can create an inhibitory postsynaptic potential, which decreases the likelihood of firing.
- Through temporal and spatial summation, the postsynaptic neuron integrates its many excitatory and inhibitory inputs.
- Regulation of synaptic activity is produced by axoaxonic synapses from other neurons, adjustment of transmitter output by autoreceptors, and change in the number or sensitivity of postsynaptic receptors.
- Leftover neurotransmitter may be taken back into the presynaptic terminals, absorbed by glial cells, or broken down by an enzyme.
- The human nervous system contains a large number of neurotransmitters, which are detected by an even greater variety of receptors. A neuron can release combinations of two or more neurotransmitters.
- The computing work of the brain is done in complex neural networks.

STUDY RESOURCES

FOR FURTHER THOUGHT

- What would be the effect if there were no constraints on the free flow of ions across the neuron membrane?
- What effect would it have on neural conduction if the action potential were decremental?

- Sports drinks replenish electrolytes that are lost during exercise. Electrolytes are compounds that separate into ions; for example, sodium chloride (table salt) dissociates into sodium and chloride ions. What implication do you think electrolyte loss might have for the nervous system? Why?
- Imagine what the effect would be if the nervous system used only one neurotransmitter.
- How similar to humans do you think computers are capable of becoming? How much is your answer based on how you think human behavior is controlled versus how capable you think computers are?

TEST YOUR UNDERSTANDING

1. Describe the ion movements and voltage changes that make up the neural impulse, from graded potential (at the axon hillock) to recovery.
2. Discuss the ways in which the synapse increases the neuron's capacity for transmitting information.
3. Describe how neurons regulate neurotransmitter amounts in the synapse and what might happen to behaviors if those processes work too well or too poorly.
4. Describe neural networks and explain their importance.

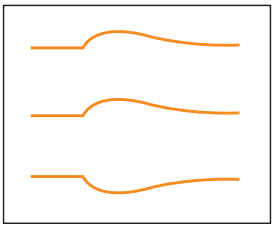
SELECT THE BEST ANSWER:

1. The inside of the neuron is relatively poor in _____ ions and rich in _____ ions.
   a. chloride, phosphate
   b. sodium, potassium
   c. potassium, sodium
   d. calcium, sodium
2. The rate law
   a. explains how the intensity of stimuli is represented.
   b. does not apply to neurons outside the brain.
   c. describes transmission in myelinated axons.
   d. describes the process of postsynaptic integration.
3. Without the sodium-potassium pump, the neuron would become
   a. more sensitive because of accumulation of sodium ions.
   b. more sensitive because of accumulation of potassium ions.
   c. overfilled with sodium ions and unable to fire.
   d. overfilled with potassium ions and unable to fire.
4. There is a limit to how rapidly a neuron can produce action potentials. This is due to
   a. inhibition.
   b. facilitation.
   c. the absolute refractory period.
   d. the relative refractory period.
5. Saltatory conduction results in
   a. less speed with the use of more energy.
   b. greater speed with the use of less energy.
   c. less speed with the use of less energy.
   d. greater speed with the use of more energy.
6. General anesthetics open potassium channels, allowing potassium ions to leak out of the neuron. This
   a. increases firing in pain-inhibiting centers in the brain.
   b. increases firing in the neuron until it is fatigued.
   c. depolarizes the neuron, preventing firing.
   d. hyperpolarizes the neuron, preventing firing.
7. When the action potential arrives at the terminal button, entry of _____ ions stimulates release of transmitter.
   a. potassium
   b. sodium
   c. calcium
   d. chloride
8. All the following neurotransmitters are deactivated by reuptake except
   a. acetylcholine.
   b. norepinephrine.
   c. serotonin.
   d. dopamine.
9. An inhibitory neurotransmitter causes the inside of the postsynaptic neuron to become
   a. more positive.
   b. more negative.
   c. more depolarized.
   d. neutral in charge.

10. Excitatory postsynaptic potentials are typically produced by movement of _____ ions, whereas inhibitory postsynaptic potentials are typically produced by movement of _____ ions.
    a. potassium; sodium or chloride
    b. potassium; sodium or calcium
    c. sodium; calcium or chloride
    d. sodium; potassium or chloride

11. Which of the following is not an example of regulation of synaptic activity?
    a. A neuron has its synapse on the terminals of another and affects its transmitter release.
    b. Autoreceptors reduce the amount of transmitter released.
    c. A presynaptic neuron inhibits a postsynaptic neuron.
    d. Postsynaptic receptors change in numbers or sensitivity.

12. The graph below shows three graded potentials occurring at the same time.



Assume that the resting potential is –70 mV and that each graded potential individually produces a 5-mV change. What is the membrane's voltage after the graded potentials arrive?
    a. –65 mV
    b. –70 mV
    c. –75 mV
    d. +75 mV

13. The presence of synapses in a neuron chain provides the opportunity for
    a. increases in conduction speed.
    b. modification of neural activity.
    c. two-way communication in a pathway.
    d. regeneration of damaged neurons.

14. Neural networks
    a. are groups of neurons that function together.
    b. are where the most complex work of the brain occurs.
    c. must connect at least two brain areas to be considered a network.
    d. All of these are true.
    e. Not all of these are true.

Answers:
1. b, 2. a, 3. c, 4. c, 5. b, 6. d, 7. c, 8. a, 9. b, 10. d, 11. c, 12. a, 13. b, 14. e.

FOR FURTHER READING

1. *Synaptic Self*, by Joseph LeDoux (Penguin Books, 2003), takes the position that "your 'self,' the essence of who you are, reflects patterns of interconnectivity between neurons in your brain." A good read by a noted neuroscientist.
2. "Astrocyte Regulation of Synaptic Behavior," by Nicola J. Allen (*Annual Review of Cell and Developmental Biology*, 2014, *30*, 439–463), synthesizes research on astrocytes' role in synapse formation and regulation of synaptic activity.
3. "From Cajal to Connectome and Beyond" (*Annual Review of Neuroscience,* 2016, *39,* 197–216) reviews the "long history of attempts to understand how the brain operates as a system," dating as far back as the fifth century.
4. Two books by Olaf Sporns, *Discovering the Human Connectome* (MIT Press, 2016) and *Networks of the Brain* (MIT Press, 2016), elaborate on topics in this chapter.
5. Sebastian Seung's book *Connectome* (Mariner Books, 2013) describes the effort to map the brain using computers and artificial intelligence; you can read a summary and review in *New Scientist*, February 4, 2012, p. 46.
6. "A Million Spiking-Neuron Integrated Circuit With a Scalable Communication Network and Interface" (*Science,* 2014, *345,* 668–673) describes an IBM/Cornell University project's brain-inspired 5.4-billion transistor computer chip that mimics 1 million neurons and 256 million synapses. As a result, it can perform human-like operations, such as analyzing video to identify people and objects.
7. *Beautiful Brain: The Drawings of Santiago Ramón y Cajal* (Abrams, 2017), by Larry Swanson, Eric Newman, et al., presents Cajal's drawings as beautiful art in their own right.

KEY TERMS

absolute refractory period 30
action potential 27
agonist 42
all-or-none law 29
antagonist 42
autoreceptor 39
axon 22
axon terminal 22
cell body 22
Dale's principle 40
dendrites 22
electrostatic pressure 26
excitatory postsynaptic potential (EPSP) 35
force of diffusion 26
glial cell 30
graded potential 29
Human Connectome Project 44
hyperpolarization 34
inhibitory postsynaptic potential (IPSP) 35
interneuron 24
ion 25
ionotropic receptor 34
metabotropic receptor 34
motor neuron 22
myelin 30
neural network 43
neuron 22
neurotoxin 28
neurotransmitter 23
node of Ranvier 31
nondecremental 29
oligodendrocyte 30
optogenetics 28
partial depolarization 34
polarization 25
postsynaptic 33
presynaptic 33
presynaptic excitation 38
presynaptic inhibition 38
rate law 30
relative refractory period 30
resting potential 25
reuptake 38
saltatory conduction 31
Schwann cell 31
sensory neuron 24
sodium-potassium pump 26
spatial summation 37
synapse 33
synaptic cleft 33
temporal summation 37
vesicle 33
voltage 25