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Nerve Cells, Neural Circuitry, and Behavior

The remarkable range of human behavior depends on a sophisticated array of sensory receptors connected to a highly flexible neural organ—the brain—that selects from among the stream of sensory signals those events in the environment that are important to the individual. In other words, the brain actively organizes perception, some of which is stored in memory for future reference, and some of which is transformed into immediate behavioral responses. All this is accomplished by interconnected nerve cells.

Individual nerve cells or neurons are the basic units of the brain. The human brain contains a huge number of these cells, on the order of 10^{11} neurons, that can be classified into at least a thousand different types. Yet the complexity of human behavior depends less on the variety of neurons than on their organization into anatomical circuits with precise functions. One key organizational principle of the brain, therefore, is that nerve cells with similar properties can produce different actions because of the way they are interconnected.

Because relatively few principles of organization give rise to considerable complexity, it is possible to learn a great deal about how the nervous system produces behavior by focusing on five basic features of the nervous system:

1. The structural components of individual nerve cells;
2. The mechanisms by which neurons produce signals within and between nerve cells;
3. The patterns of connections between nerve cells and between nerve cells and their targets: muscles and gland effectors;
4. The relationship of different patterns of interconnection to different types of behavior; and
5. How neurons and their connections are modified by experience

The various parts of this book are organized around these five major topics. In this chapter we provide an overview of the neural control of behavior by introducing these topics together. We first consider the structure and function of neurons and the glial cells that surround and support them. We then examine how individual cells organize and transmit signals and how signaling

between a few interconnected nerve cells produces a simple behavior, the knee-jerk reflex. Finally, we consider how changes in signaling by specific cells can modify behavior.

The Nervous System Has Two Classes of Cells

There are two main classes of cells in the nervous system: nerve cells, or neurons, and glial cells, or glia.

Nerve Cells Are the Signaling Units of the Nervous System

A typical neuron has four morphologically defined regions: (1) the cell body, (2) dendrites, (3) axon, and (4) presynaptic terminals (Figure 2–1). As we shall see later, each region has a distinct role in generating signals and communicating with other nerve cells.

The cell body or *soma* is the metabolic center of the cell. It contains the nucleus, which contains the genes of the cell, and the endoplasmic reticulum, an extension of the nucleus where the cell's proteins are synthesized. The cell body usually gives rise to two kinds of processes: several short *dendrites* and one long, tubular *axon*. Dendrites branch out in tree-like fashion and are the main apparatus for receiving incoming signals from other nerve cells. The axon typically extends some distance from the cell body and carries signals to other neurons. An axon can convey electrical signals over distances ranging from 0.1 mm to 2 m. These electrical signals, called *action potentials,* are initiated at a specialized trigger region near the origin of the axon

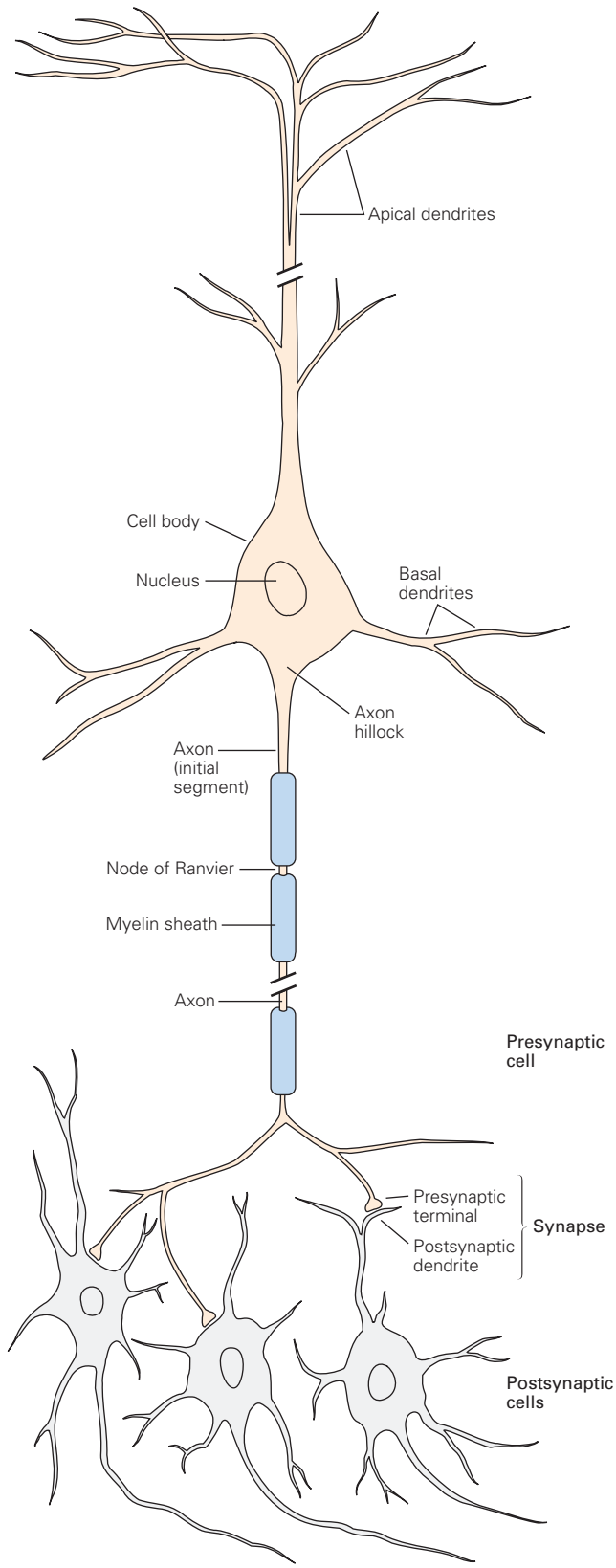

Figure 2–1 The structure of a neuron. Most neurons in the vertebrate nervous system have several main features in common. The cell body contains the nucleus, the storehouse of genetic information, and gives rise to two types of cell processes: axons and dendrites. Axons are the transmitting element of neurons; they vary greatly in length, some extending more than 2 m within the body. Most axons in the central nervous system are very thin (between 0.2 μm and 20 μm in diameter) compared with the diameter of the cell body (50 μm or more). Many axons are insulated by a sheath of fatty myelin that is regularly interrupted at gaps called the nodes of Ranvier. The action potential, the cell's conducting signal, is initiated at the initial segment of the axon and propagates to the synapse, the site at which signals flow from one neuron to another. Branches of the axon of the presynaptic neuron transmit signals to the postsynaptic cell. The branches of a single axon may form synapses with as many as 1,000 postsynaptic neurons. The apical and basal dendrites together with the cell body are the input elements of the neuron, receiving signals from other neurons.

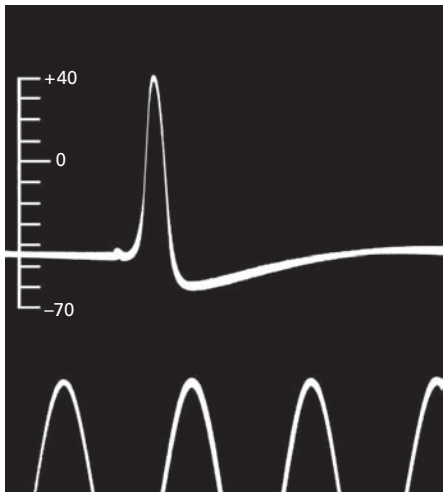

Figure 2–2 This historic tracing is the first published intracellular recording of an action potential. It was recorded in 1939 by Hodgkin and Huxley from a squid giant axon, using glass capillary electrodes filled with sea water. The timing pulses are separated by 2 ms. The vertical scale indicates the potential of the internal electrode in millivolts, the sea water outside being taken as zero potential. (Reproduced, with permission, from Hodgkin and Huxley 1939.)

called the *initial segment* from which they propagate down the axon without failure or distortion at speeds of 1 to 100 m/s. The amplitude of an action potential traveling down the axon remains constant at 100 mV because the action potential is an all-or-none impulse that is regenerated at regular intervals along the axon (Figure 2–2).

Action potentials are the signals by which the brain receives, analyzes, and conveys information. These signals are highly stereotyped throughout the nervous system, even though they are initiated by a great variety of events in the environment that impinge on our bodies—from light to mechanical contact, from odorants to pressure waves. The signals that convey information about vision are identical to those that carry information about odors. Here we see a key principle of brain function: the information conveyed by an action potential is determined not by the form of the signal but by the pathway the signal travels in the brain. The brain analyzes and interprets patterns of incoming electrical signals and their pathways, and in turn creates our sensations of sight, touch, smell, and sound.

To increase the speed by which action potentials are conducted, large axons are wrapped in an insulating sheath of a lipid substance, *myelin*. The sheath is interrupted at regular intervals by the nodes of Ranvier, uninsulated spots on the axon where the action potential is regenerated. We shall learn more about myelination in Chapter 4 and about action potentials in Chapter 7.

Near its end the axon divides into fine branches that contact other neurons at specialized zones of communication known as *synapses*. The nerve cell transmitting a signal is called the *presynaptic cell*; the cell receiving the signal is the *postsynaptic cell*. The presynaptic cell transmits signals from specialized enlarged regions of its axon's branches, called *presynaptic terminals* or *nerve terminals*. The presynaptic and postsynaptic cells are separated by a very narrow space, the *synaptic cleft*. Most presynaptic terminals end on the postsynaptic neuron's dendrites; but the terminals may also terminate on the cell body or, less often, at the beginning or end of the axon of the receiving cell (see Figure 2–1).

As we saw in Chapter 1, Ramón y Cajal provided much of the early evidence for the neuron doctrine, the principle that each neuron is a discrete cell with distinctive processes arising from its cell body and that neurons are the signaling units of the nervous system. In retrospect it is hard to appreciate how difficult it was to persuade scientists of this elementary idea. Unlike other tissues, whose cells have simple shapes and fit into a single field of the light microscope, nerve cells have complex shapes. The elaborate patterns of dendrites and the seemingly endless course of some axons initially made it extremely difficult to establish a relationship between these elements. Even after the anatomists Jacob Schleiden and Theodor Schwann put forward the cell theory in the early 1830s—and the idea that cells are the structural units of all living matter became a central dogma of biology—most anatomists did not accept that the cell theory applied to the brain, which they thought of as a continuous, web-like reticulum of very thin processes.

The coherent structure of the neuron did not become clear until late in the 19th century, when Ramón y Cajal began to use the silver-staining method introduced by Golgi. Still used today, this method has two advantages. First, in a random manner that is not understood, the silver solution stains only about 1% of the cells in any particular brain region, making it possible to examine a single neuron in isolation from its neighbors. Second, the neurons that do take up the stain are delineated in their entirety, including the cell body, axon, and full dendritic tree. The stain reveals that there is no cytoplasmic continuity between neurons, even at synapses between two cells.

Ramón y Cajal applied Golgi's method to the embryonic nervous systems of many animals as well as humans.

By examining the structure of neurons in almost every region of the nervous system, he could describe classes of nerve cells and map the precise connections between many of them. In this way Ramón y Cajal adduced, in addition to the neuron doctrine, two other principles of neural organization that would prove particularly valuable in studying communication in the nervous system.

The first of these has come to be known as the *principle of dynamic polarization.* It states that electrical signals within a nerve cell flow only in one direction: from the receiving sites of the neuron, usually the dendrites and cell body, to the trigger region at the axon. From there the action potential is propagated along the entire length of the axon to its terminals. In most neurons studied to date electrical signals in fact travel in one direction. Later in this chapter we describe the physiological basis of this principle.

The other principle advanced by Ramón y Cajal is that of *connectional specificity,* which states that nerve cells do not connect randomly with one another in the formation of networks. Rather each cell makes specific connections—at particular contact points—with certain postsynaptic target cells but not with others. The principles of dynamic polarization and connectional specificity are the basis of the modern connectionist approach to studying the brain.

Ramón y Cajal was also among the first to realize that the feature that most distinguishes one type of neuron from another is form, specifically the number of the processes arising from the cell body. Neurons are thus classified into three large groups: unipolar, bipolar, and multipolar.

Unipolar neurons are the simplest because they have a single primary process, which usually gives rise to many branches. One branch serves as the axon; other branches function as receiving structures (Figure 2–3A). These cells predominate in the nervous systems of invertebrates; in vertebrates they occur in the autonomic nervous system.

Bipolar neurons have an oval soma that gives rise to two distinct processes: a dendritic structure that receives signals from the periphery of the body and an axon that carries information toward the central nervous system (Figure 2–3B). Many sensory cells are bipolar, including those in the retina and in the olfactory epithelium of the nose. The receptor neurons that convey touch, pressure, and pain signals to the spinal cord, are variants of bipolar cells called *pseudo-unipolar* cells. These cells develop initially as bipolar cells but the two cell processes fuse into a single continuous structure that emerges from a single point in the cell body. The axon splits into two branches, one running to the periphery (to sensory receptors in the skin, joints, and muscle) and another to the spinal cord (Figure 2–3C).

Multipolar neurons predominate in the nervous system of vertebrates. They typically have a single axon and many dendritic structures emerging from various points around the cell body (Figure 2–3D). Multipolar cells vary greatly in shape, especially in the length of their axons and in the extent, dimensions, and intricacy of their dendritic branching. Usually the extent of branching correlates with the number of synaptic contacts that other neurons make onto them. A spinal motor neuron with a relatively modest number of dendrites receives about 10,000 contacts—1,000 on the cell body and 9,000 on dendrites. The dendritic tree of a Purkinje cell in the cerebellum is much larger and bushier, receiving as many as a million contacts!

Nerve cells are also classified into three major functional categories: sensory neurons, motor neurons, and interneurons. Sensory neurons carry information from the body's peripheral sensors into the nervous system for the purpose of both perception and motor coordination. Some primary sensory neurons are called afferent neurons, and the two terms are used interchangeably. The term *afferent* (carried toward the central nervous system) applies to all information reaching the central nervous system from the periphery, whether or not this information leads to sensation. The term *sensory* should, strictly speaking, be applied only to afferent inputs that lead to perception. Motor neurons carry commands from the brain or spinal cord to muscles and glands (efferent information). Interneurons are the most numerous and are subdivided into two classes: relay and local. Relay or projection interneurons have long axons and convey signals over considerable distances, from one brain region to another. Local interneurons have short axons because they form connections with nearby neurons in local circuits.

Each functional classification can be subdivided further. Sensory system interneurons can be classified according to the type of sensory stimuli to which they respond; these initial classifications can be broken down still further, into many subgroups according to location, density, and size. For example, the retinal ganglion cell interneurons, which respond to light, are classified into 13 types based on the size of the dendritic tree, the branching density, and the depth of its location in specific layers of the retina (Figure 2–4).

Glial Cells Support Nerve Cells

Glial cells greatly outnumber neurons—there are 2 to 10 times more glia than neurons in the vertebrate central nervous system. The name for these cells derives

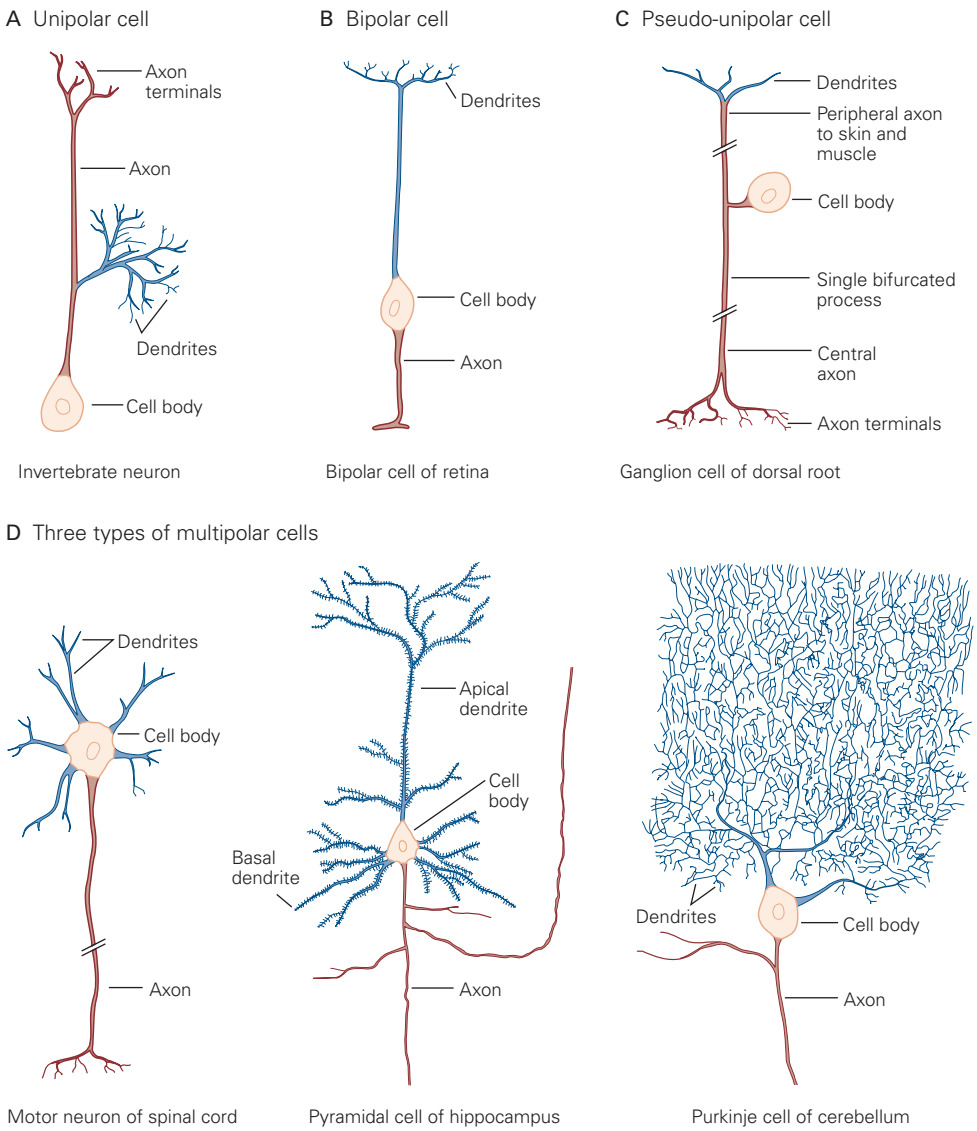

Figure 2–3 Neurons are classified as unipolar, bipolar, or multipolar according to the number of processes that originate from the cell body.

A. Unipolar cells have a single process emanating from the cell. Different segments serve as receptive surfaces or releasing terminals. Unipolar cells are characteristic of the invertebrate nervous system.

B. Bipolar cells have two types of processes that are functionally specialized. The dendrite receives electrical signals and the axon transmits signals to other cells.

C. Pseudo-unipolar cells are variants of bipolar cells that carry somatosensory information to the spinal cord. During development the two processes of the embryonic bipolar cell fuse and emerge from the cell body as a single process that has two functionally distinct segments. Both segments function as axons; one extends to peripheral skin or muscle, the other to the central spinal cord. (Adapted, with permission, from Ramón y Cajal 1933.)

D. Multipolar cells have a single axon and many dendrites. They are the most common type of neuron in the mammalian nervous system. Three examples illustrate the large diversity of these cells. Spinal motor neurons innervate skeletal muscle fibers. Pyramidal cells have a roughly triangular cell body; dendrites emerge from both the apex (the apical dendrite) and the base (the basal dendrites). Pyramidal cells are found in the hippocampus and throughout the cerebral cortex. Purkinje cells of the cerebellum are characterized by a rich and extensive dendritic tree that accommodates an enormous synaptic input. (Adapted, with permission, from Ramón y Cajal 1933.)

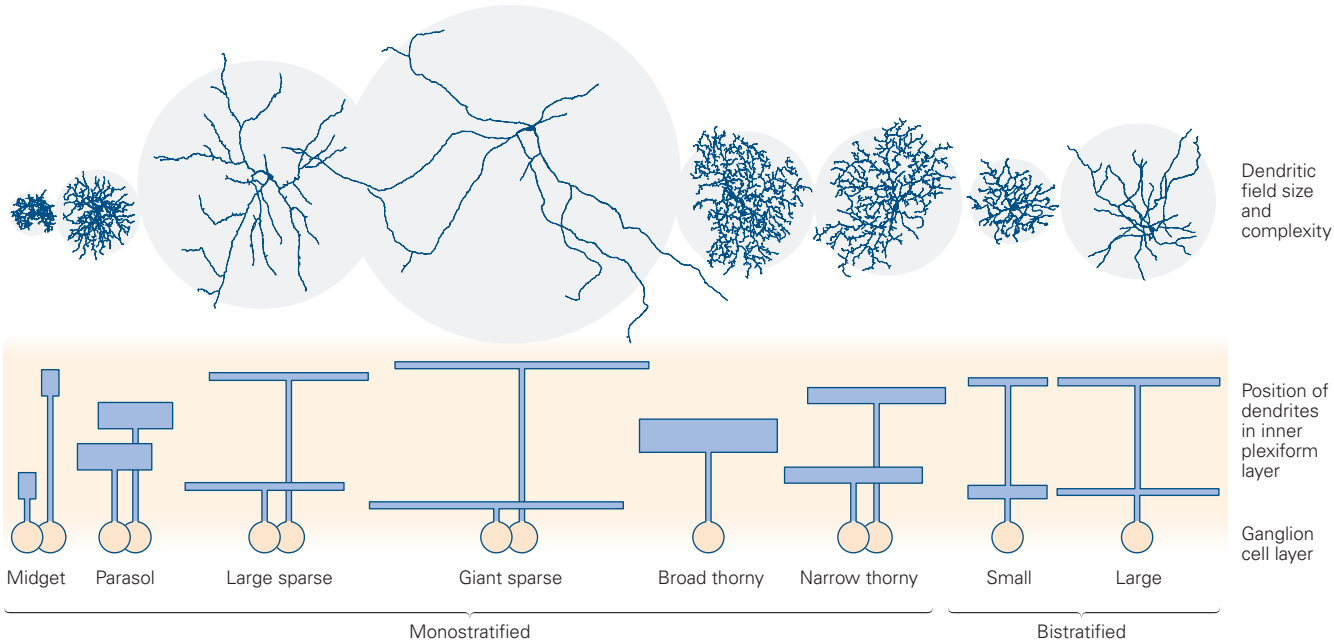

Figure 2–4 Sensory neurons can be subdivided into functionally distinct groups. Photodynamic staining distinguishes 13 types of retinal ganglion cells on the basis of their dendritic shape and depth of position in the retina. (Reproduced, with permission, from Dacey et al. 2003.)

from the Greek for glue, but glia do not commonly hold nerve cells together. Rather, they surround the cell bodies, axons, and dendrites of neurons. Glia differ from neurons morphologically; they do not form dendrites and axons. Glia also differ functionally. Although they arise from the same embryonic precursor cells, they do not have the same membrane properties as neurons; are not electrically excitable; and are not directly involved in electrical signaling, which is the function of nerve cells.

There are many kinds of glial cells. As we will discuss in Chapter 4, the diversity in morphology of glial cells suggests that glia are probably as heterogeneous as neurons. Nonetheless, glia in the vertebrate nervous system can be divided into two major classes: microglia and macroglia. Microglia are immune system cells that are mobilized to present antigens and become phagocytes during injury, infection, or degenerative diseases. There are three main types of macroglia: oligodendrocytes, Schwann cells, and astrocytes. In the human brain about 80% of all the cells are macroglia. Of these, approximately half are oligodendrocytes and half are astrocytes.

Oligodendrocytes and Schwann cells are small cells with relatively few processes. Both cells form the myelin sheath that insulates an axon by tightly winding their membranous processes around the axon in a spiral. Oligodendrocytes are found in the central nervous system; each cell envelops from one to 30 axonal segments (called internodes), depending on axon diameter (Figure 2–5A). Schwann cells occur in the peripheral nervous system, where each envelops a single segment of one axon (Figure 2–5B). Upon myelination, oligodendrocytes and Schwann cells influence axons by enhancing signal conduction and by segregating voltage-sensitive ion channels into distinct axonal domains (called node of Ranvier).

Astrocytes, the third main class of glial cells, owe their name to their irregular, roughly star-shaped cell bodies and large numbers of processes (Figure 2–5C). They comprise two major types. Protoplasmic astrocytes are found in the gray matter; their many processes end in sheet-like appendages. Fibrous astrocytes are found in the white matter and have long, fine processes that contain large bundles of tightly packed intermediate filaments. Both types of astrocytes have end-feet, dilatations that contact and surround capillaries and arterioles throughout the brain (Figure 2–5C). The sheet-like processes of protoplasmic astrocytes envelop nerve cell bodies and synapses, whereas the end-feet of fibrous astrocytes contact axons at the nodes of Ranvier.

The functions of astrocytes are still mysterious. It is generally thought that astrocytes are not essential

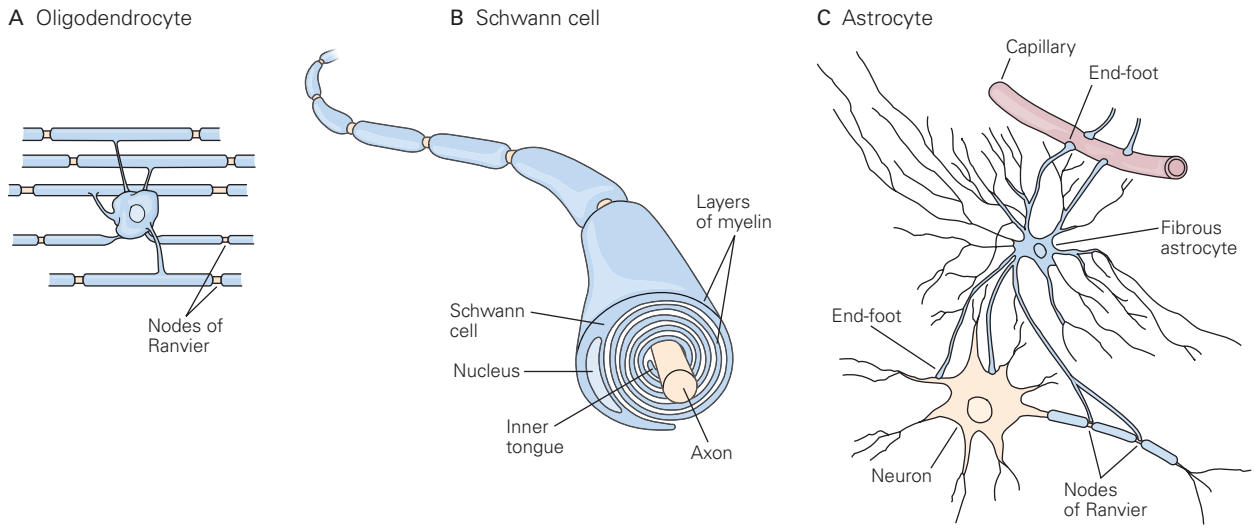

Figure 2–5 The principal types of glial cells are oligodendrocytes and astrocytes in the central nervous system and Schwann cells in the peripheral nervous system.

A. Oligodendrocytes are small cells with relatively few processes. In the white matter of the brain, as shown here, they provide the myelin sheaths that insulate axons. A single oligodendrocyte can wrap its membranous processes around many axons. In the gray matter perineural oligodendrocytes surround and support the cell bodies of neurons.

B. Schwann cells furnish the myelin sheaths for axons in the peripheral nervous system. During development several Schwann cells are positioned along the length of a single axon. Each cell forms a myelin sheath approximately 1 mm long between two nodes of Ranvier. The sheath is formed as the inner tongue of the Schwann cell turns around the axon several times, wrapping the axon in layers of membrane. In actuality the layers of myelin are more compact than what is shown here. (Adapted, with permission, from Alberts et al. 2002.)

C. Astrocytes, a major class of glial cells in the central nervous system, are characterized by their star-like shape and the broad end-feet on their processes. Because these end-feet put the astrocyte into contact with both capillaries and neurons, astrocytes are thought to have a nutritive function. Astrocytes also play an important role in maintaining the blood-brain barrier (See Appendix D).

for information processing but support neurons in four ways:

1. Astrocytes separate cells, thereby insulating neuronal groups and synaptic connections from each other.
2. Because astrocytes are highly permeable to K^+, they help regulate the K^+ concentration in the space between neurons. As we shall learn below, K^+ flows out of neurons when they fire. Repetitive firing may create excess extracellular K^+ that could interfere with signaling between cells in the vicinity. Astrocytes can take up the excess K^+ and thus maintain the efficiency of signaling between neurons.
3. Astrocytes perform other important housekeeping chores that promote efficient signaling between neurons. For example, as we shall learn later, they take up neurotransmitters from synaptic zones after release.
4. Astrocytes help nourish surrounding neurons by releasing growth factors.

Although glial cells do not generate action potentials, they have recently been found to participate in neuron-glial signaling processes. The significance of this signaling is still poorly understood, but it may actively help regulate synapse development and function (Chapter 4).

Each Nerve Cell Is Part of a Circuit That Has One or More Specific Behavioral Functions

Every behavior is mediated by specific sets of interconnected neurons, and every neuron's behavioral function is determined by its connections with other neurons. We can illustrate this with a simple behavior, the knee-jerk reflex. The reflex is initiated when a transient imbalance of the body stretches the quadriceps extensor muscles of the leg. This stretching elicits sensory information that is conveyed to motor neurons, which in turn sends commands to the extensor muscles to contract so that balance is restored. This reflex is useful for clinically, but the underlying mechanism

is important because it continuously maintains normal tone in the quadriceps and prevents our knees from buckling when we stand or walk.

The tendon of the quadriceps femoris, an extensor muscle that moves the lower leg, is attached to the tibia through the tendon of the kneecap. Tapping this tendon just below the patella stretches the quadriceps femoris. This stretch initiates reflex contraction of the quadriceps muscle to produce the familiar knee jerk. By increasing the tension of a select group of muscles, the stretch reflex changes the position of the leg, suddenly extending it outward (Figure 2–6).

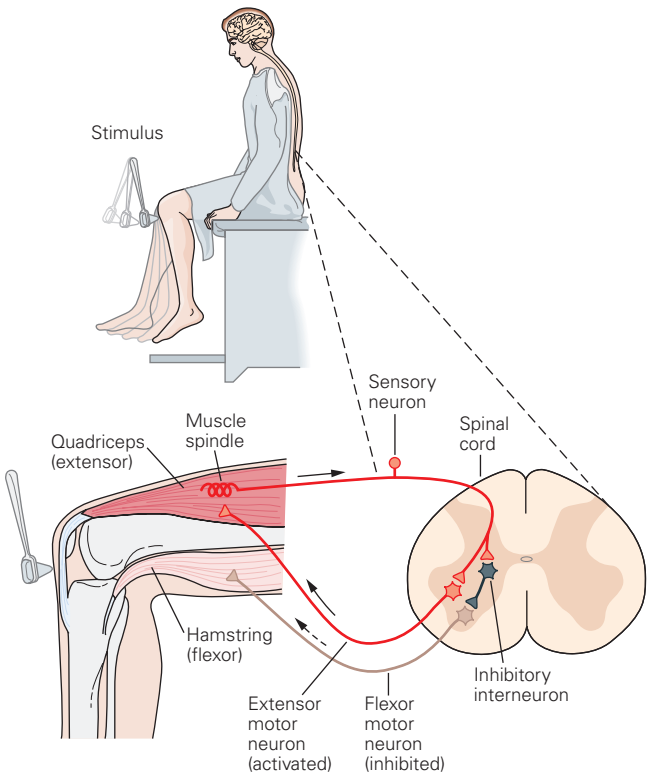

Figure 2–6 The knee-jerk reflex is controlled by a simple circuit of sensory and motor neurons. Tapping the kneecap with a reflex hammer pulls on the tendon of the quadriceps femoris, a muscle that extends the lower leg. When the muscle stretches in response to the pull of the tendon, information regarding this change in the muscle is conveyed to the central nervous system by sensory neurons. In the spinal cord the sensory neurons form excitatory synapses with extensor motor neurons that contract the quadriceps, the muscle that was stretched. The sensory neurons act indirectly, through interneurons, to inhibit flexor motor neurons that would otherwise contract the opposing muscle, the hamstring. These actions combine to produce the reflex behavior. In the drawing each extensor and flexor motor neuron represents a population of many cells.

The cell bodies of the sensory neurons involved in the knee-jerk reflex are clustered near the spinal cord in the dorsal root ganglia. They are pseudo-unipolar cells; one branch of each cell's axon runs to the quadriceps muscle at the periphery, whereas the other runs centrally into the spinal cord. The branch that innervates the quadriceps makes contact with stretch-sensitive receptors (muscle spindles) and is excited when the muscle is stretched. The branch reaching the spinal cord forms excitatory connections with the motor neurons that innervate the quadriceps and control its contraction. This branch also contacts local interneurons that *inhibit* the motor neurons controlling the opposing flexor muscles (Figure 2–6). These local interneurons are not involved in producing the stretch reflex itself, but by coordinating motor action they increase the stability of the reflex. Thus the electrical signals that produce the stretch reflex carry four kinds of information:

1. Sensory information is conveyed to the central nervous system (the spinal cord) from muscle.
2. Motor commands from the central nervous system are issued to the muscles that carry out the knee jerk.
3. Inhibitory commands are issued to motor neurons that innervate opposing muscles, providing coordination of muscle action.
4. Information about local neuronal activity related to the knee jerk is sent to higher centers of the central nervous system, permitting the brain to coordinate different behaviors either simultaneously or in series.

The stretching of just one muscle, the quadriceps, activates several hundred sensory neurons, each of which makes direct contact with 45 to 50 motor neurons. This pattern of connection, in which one neuron activates many target cells, is called *divergence* (Figure 2–7A). It is especially common in the input stages of the nervous system; by distributing its signals to many target cells, a single neuron can exert wide and diverse influence. Conversely, a single motor cell in the knee jerk circuit receives 200 to 450 input contacts from approximately 130 sensory cells. This pattern of connection is called *convergence* (Figure 2–7B). It is common at the output stages of the nervous system; a target motor cell that receives information from many sensory neurons is able to integrate information from many sources. Convergence also ensures that a motor neuron is activated only if a sufficient number of sensory neurons become activated together.

A stretch reflex such as the knee-jerk reflex is a simple behavior produced by two classes of neurons

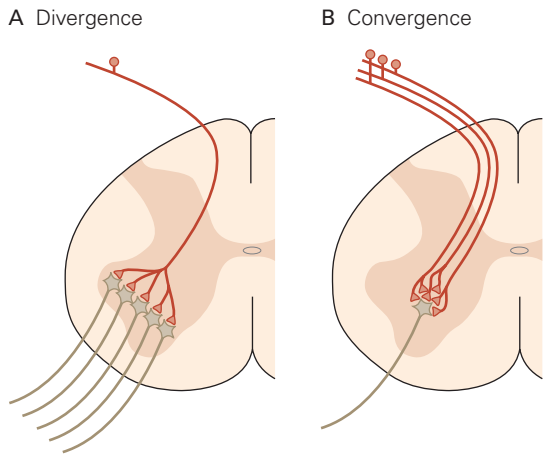

Figure 2–7 Diverging and converging neuronal connections are a key organizational feature of the brain.

A. In the sensory systems each receptor neuron usually contacts several neurons that represent the second stage of processing. At subsequent processing stages the incoming connections diverge even more. This allows sensory information from a single site to be distributed more widely in the spinal cord and brain.

B. By contrast, motor neurons are the targets of progressively converging connections. With this arrangement input from many presynaptic cells is required to activate the motor neuron.

Signaling Is Organized in the Same Way in All Nerve Cells

To produce a behavior, a stretch reflex for example, each participating sensory and motor nerve cell must generate four different signals in sequence, each at different site within the cell: an input signal, a trigger signal, a conducting signal, and an output signal. Regardless of cell size and shape, transmitter biochemistry, or behavioral function, almost all neurons can be described by a model neuron that has four functional

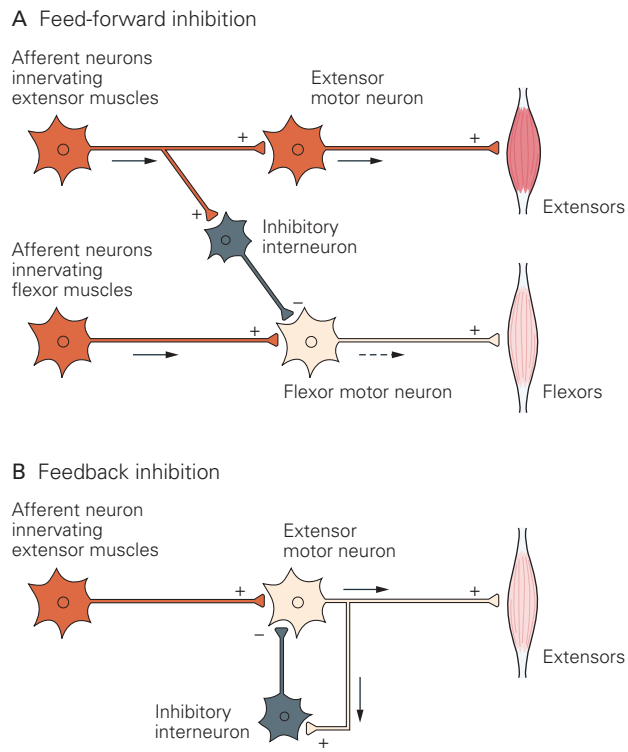

Figure 2–8 Inhibitory interneurons can produce either feed-forward or feedback inhibition.

A. Feed-forward inhibition enhances the effect of the active pathway by suppressing the activity of pathways mediating opposing actions. Feed-forward inhibition is common in monosynaptic reflex systems. For example, in the knee-jerk reflex circuit (Figure 2–6) afferent neurons from extensor muscles excite not only the extensor motor neurons but also inhibitory interneurons that prevent the firing of the motor cells innervating the opposing flexor muscles.

B. Feedback inhibition is a self-regulating mechanism. Here extensor motor neurons act on inhibitory interneurons that in turn act on the extensor motor neurons themselves and thus reduce their probability of firing. The effect is to dampen activity within the stimulated pathway and prevent it from exceeding a certain critical level.

connecting at excitatory synapses. But not all important signals in the brain are excitatory. Many neurons produce inhibitory signals that reduce the likelihood of firing. Even in the simple knee-jerk reflex the sensory neurons make both excitatory and inhibitory connections. Excitatory connections in the leg's extensor muscles cause these muscles to contract, whereas connections with inhibitory interneurons prevent the antagonist flexor muscles from contracting. This feature of the circuit is an example of *feed-forward inhibition* (Figure 2–8A). In the knee-jerk reflex, feed-forward inhibition is *reciprocal*, ensuring that the flexor and extensor pathways always inhibit each other so that only muscles appropriate for the movement and not those opposed to it are recruited.

Neurons can also have connections that provide *feedback inhibition*. For example, a motor neuron may have excitatory connections with both a muscle and an inhibitory interneuron that in turn inhibits the motor neuron. The inhibitory interneuron is thus able to limit the ability of the motor neuron to excite the muscle (Figure 2–8B). We will encounter many examples of feed-forward and feedback inhibition when we examine more complex behaviors in later chapters.

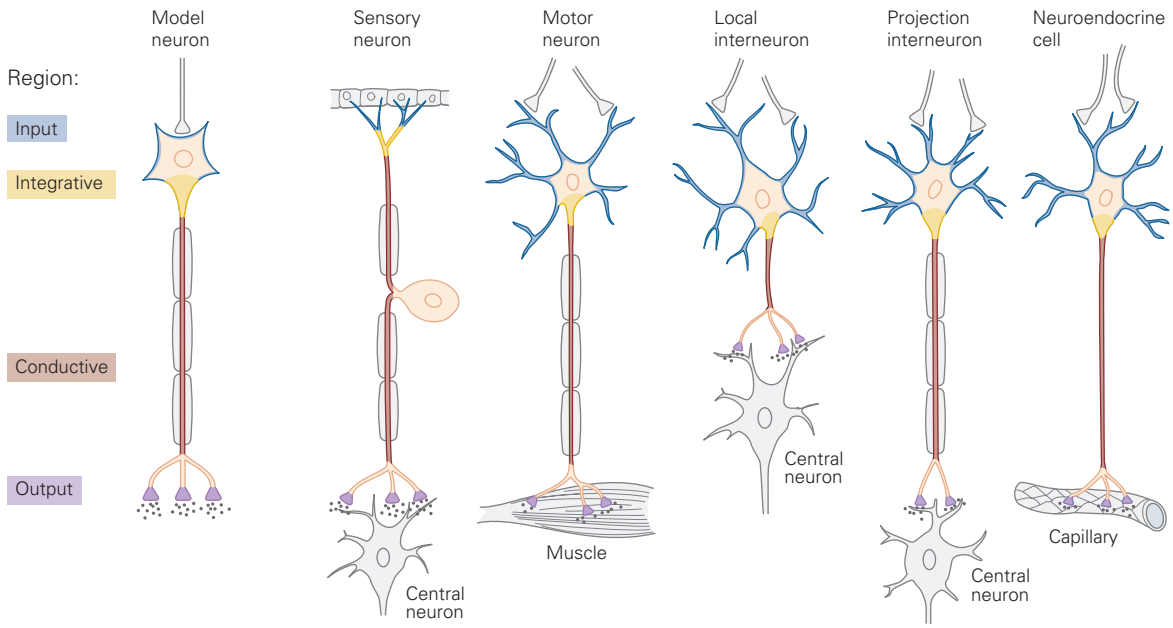

Figure 2–9 Most neurons, regardless of type, have four functional regions in which different types of signals are generated. Thus the functional organization of most neurons can be represented schematically by a model neuron. The input, integrative, and conductive signals are all electrical and integral to the cell, whereas the output signal is a chemical substance ejected by the cell into the synaptic cleft. Not all neurons share all these features; for example, local interneurons often lack a conductive component.

components that generate the four types of signals: a receptive component, a summing or integrative component, a long-range signaling component, and a secretory component (Figure 2–9). This model neuron is the physiological expression of Ramón y Cajal's principle of dynamic polarization.

The different types of signals generated in a neuron are determined in part by the electrical properties of the cell membrane. Every cell, including a neuron, maintains a certain difference in the electrical potential on either side of the plasma membrane when the cell is at rest. This is called the *resting membrane potential*. In a typical resting neuron the voltage of the inside of the cell is about 65 mV more negative than the voltage outside the cell. Because the voltage outside the membrane is defined as zero, we say the resting membrane potential is –65 mV. The resting potential in different nerve cells ranges from –40 to –80 mV; in muscle cells it is greater still, about –90 mV. As we shall see in Chapter 6, the resting membrane potential results from two factors: the unequal distribution of electrically charged ions, in particular the positively charged Na^+ and K^+ ions, and the selective permeability of the membrane.

The unequal distribution of positively charged ions on either side of the cell membrane is maintained by two main mechanisms. Intracellular Na^+ and K^+ concentrations are largely controlled by a membrane protein that actively pumps Na^+ out of the cell and K^+ back into it. This *Na^+-K^+ pump,* about which we shall learn more in Chapter 6, keeps the Na^+ concentration in the cell low (about one-tenth the concentration outside the cell) and the K^+ concentration high (about 20 times the concentration outside). The extracellular concentrations of Na^+ and K^+ are maintained by the kidneys.

The cell membrane is selectively permeable to K^+ because the otherwise impermeable membrane contains proteins that form pores called *ion channels.* The channels that are active when the cell is at rest are highly permeable to K^+ but considerably less permeable to Na^+. The K^+ ions tend to leak out of these open channels, down the ion's concentration gradient. As K^+ ions exit the cell, they leave behind a cloud of unneutralized negative charge on the inner surface of the membrane, so that the net charge inside the membrane is more negative than that outside.

A cell, such as nerve and muscle, is said to be excitable when its membrane potential can be quickly and significantly altered. This change serves as a signaling mechanism. In some neurons reducing the membrane potential by 10 mV (from –65 to –55 mV) makes the

membrane much more permeable to Na^+ than to K^+. The resultant influx of positively charged Na^+ neutralizes the negative charge inside the cell and causes a brief and explosive change in membrane potential to +40 mV. This *action potential* is conducted down the cell's axon to the axon's terminal, where it initiates an elaborate chemical communication with other neurons or muscle cells. The action potential is actively propagated along the axon so that its amplitude does not diminish by the time it reaches the axon terminal. An action potential typically lasts approximately 1 ms, after which the membrane returns to its resting state, with its normal separation of charges and higher permeability to K^+ than to Na^+.

We shall learn more about the mechanisms underlying the resting potential and action potential in Chapters 6 to 7. In addition to the long distance signals represented by the action potential, nerve cells also produce local signals—receptor potentials and synaptic potentials—that are not actively propagated and that typically decay within just a few millimeters.

The change in membrane potential that generates long-range and local signals can be either a decrease or an increase from the resting potential. The resting membrane potential therefore provides the baseline on which all signaling occurs. A reduction in membrane potential is called *depolarization*. Because depolarization enhances a cell's ability to generate an action potential, it is excitatory. In contrast, an increase in membrane potential is called *hyperpolarization*. Hyperpolarization makes a cell less likely to generate an action potential and is therefore inhibitory.

The Input Component Produces Graded Local Signals

In most neurons at rest no current flows from one part of the cell to another, so the resting potential is the same throughout. In sensory neurons current flow is typically initiated by a physical stimulus, which activates specialized receptor proteins at the neuron's receptive surface. In our example of the knee-jerk reflex, stretching of the muscle activates specific ion channels that open in response to stretch of the sensory neuron membrane, as we shall learn in Chapter 5. The opening of these channels when the cell is stretched permits the rapid influx of Na^+ ions into the sensory cell. This ionic current changes the membrane potential, producing a local signal called the *receptor potential*.

The amplitude and duration of a receptor potential depend on the intensity of the muscle stretch: The larger or longer-lasting the stretch, the larger or longer-lasting the resulting receptor potential (Figure 2–10A). Thus, unlike the action potential, which is all or none, receptor potentials are graded. Most receptor potentials are depolarizing (excitatory). However, hyperpolarizing (inhibitory) receptor potentials are found in the retina.

The receptor potential is the first representation of stretch to be coded in the nervous system. This signal spreads passively, however, and therefore does not travel much farther than 1 to 2 mm. In fact, 1 mm down the axon the amplitude of the signal is only about one-third what it was at the site of generation. To be carried successfully to the central nervous system, the local signal must be amplified—it must generate an action potential. In the knee-jerk reflex the receptor potential in the sensory neuron must reach the first node of Ranvier in the axon. If it is large enough, the signal triggers an action potential that then propagates without failure to the axon terminals in the spinal cord (Figure 2–10C). At the synapse between the sensory neuron and a motor neuron, the action potential produces a chain of events that results in an input signal to the motor neuron.

In the knee-jerk reflex the action potential in the presynaptic terminal of the sensory neuron initiates the release of a chemical substance, or neurotransmitter, into the synaptic cleft (Figure 2–10D). After diffusing across the cleft, the transmitter binds to receptor proteins in the postsynaptic membrane of the motor neuron, thereby directly or indirectly opening ion channels. The ensuing flow of current alters the membrane potential of the motor cell, a change called the *synaptic potential*.

Like the receptor potential, the synaptic potential is graded; its amplitude depends on how much transmitter is released. In the same cell the synaptic potential can be either depolarizing or hyperpolarizing depending on the type of receptor molecule that is activated. Synaptic potentials, like receptor potentials, spread passively and thus are local changes in potential unless the signal reaches beyond the axon's initial segment and thus can give rise to an action potential. The features of receptor and synaptic potentials are summarized in Table 2–1.

The Trigger Zone Makes the Decision to Generate an Action Potential

Sherrington first pointed out that the function of the nervous system is to weigh the consequences of different types of information and then decide on appropriate responses. This *integrative* function of the nervous system is clearly seen in the actions of the trigger zone of the neuron, the initial segment of the axon.

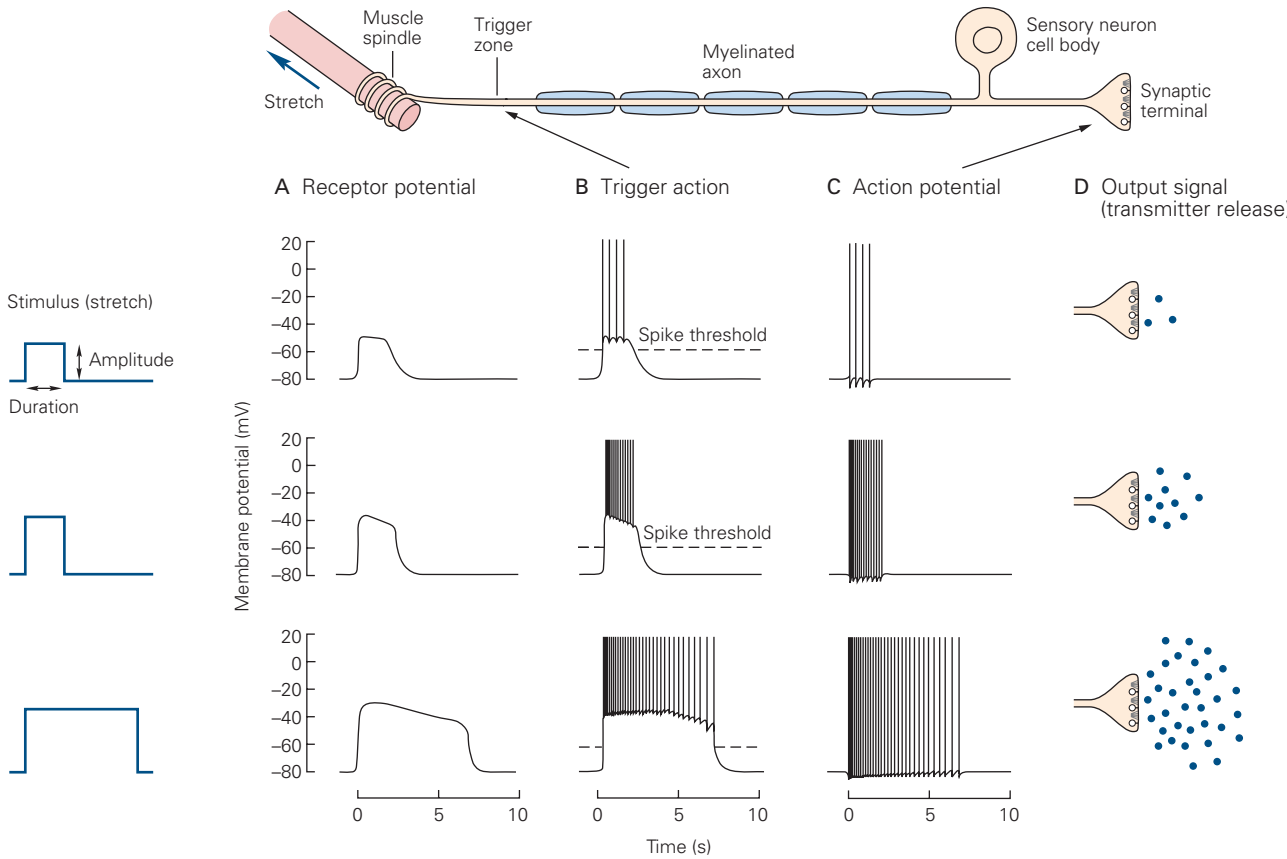

Figure 2–10 **Each of the neuron's four signaling components produces a characteristic signal.** The figure shows a sensory neuron activated by stretching of a muscle, which the neuron senses through a specialized receptor, the muscle spindle.

A. The input signal, called a receptor potential, is graded in amplitude and duration, proportional to the amplitude and duration of the stimulus.

B. The trigger zone sums the depolarization generated by the receptor potential. An action potential is generated only if the receptor potential exceeds a certain voltage threshold. Once this threshold is surpassed, any further increase in amplitude of the receptor potential can only increase the frequency with which the action potentials are generated, because action potentials have a constant amplitude. The duration of the receptor potential determines the duration of the train of action potentials. Thus the graded amplitude and duration of the receptor potential is translated into a frequency code in the action potentials generated at the trigger zone. All action potentials produced are propagated faithfully along the axon.

C. Action potentials are all-or-none. Because all action potentials have a similar amplitude and duration, the frequency and duration of firing represents the information carried by the signal.

D. When the action potential reaches the synaptic terminal, it initiates the release of a neurotransmitter, the chemical substance that serves as the output signal. The frequency of action potentials determines exactly how much neurotransmitter is released by the cell.

Action potentials are generated by a sudden influx of Na^+ through channels in the cell membrane that open and close in response to changes in membrane potential. When an input signal (a receptor potential or synaptic potential) depolarizes an area of membrane, the local change in membrane potential opens local Na^+ channels that allow Na^+ to flow down its concentration gradient, from outside the cell where the Na^+ concentration is high to inside where it is low.

Because the initial segment of the axon has the highest density of voltage-sensitive Na^+ channels and therefore the lowest threshold for generating an action potential, an input signal spreading passively along the cell membrane is more likely to give rise to an action potential at the initial segment than at other sites in the cell. This part of the axon is therefore known as the *trigger zone*. It is here that the activity of all receptor (or synaptic) potentials is summed and where, if the

Table 2–1 Comparison of Local (Passive) and Propagated Signals

Signal type	Amplitude (mV)	Duration	Summation	Effect of signal	Type of propagation
Local (passive) signals					
Receptor potentials	Small (0.1–10)	Brief (5–100 ms)	Graded	Hyperpolarizing or depolarizing	Passive
Synaptic potentials	Small (0.1–10)	Brief to long (5 ms–20 min)	Graded	Hyperpolarizing or depolarizing	Passive
Propagated (active) signals					
Action potentials	Large (70–110)	Brief (1–10 ms)	All-or-none	Depolarizing	Active

sum of the input signals reaches threshold, the neuron generates an action potential.

The Conductive Component Propagates an All-or-None Action Potential

The action potential is all-or-none: Stimuli below the threshold do not produce a signal, but stimuli above the threshold all produce the signals of the same amplitude. However much the stimuli vary in intensity or duration, the amplitude and duration of each action potential are pretty much the same. In addition, unlike receptor and synaptic potentials, which spread passively and decrease in amplitude, the action potential does not decay as it travels along the axon to its target—a distance that can be as great as 2 m—because it is periodically regenerated. This conducting signal can travel at rates as fast as 100 m/s.

The remarkable feature of action potentials is that they are highly stereotyped, varying only subtly (but in some cases importantly) from one nerve cell to another. This feature was demonstrated in the 1920s by Edgar Adrian, one of the first to study the nervous system at the cellular level. Adrian found that all action potentials have a similar shape or wave-form (see Figure 2–2). Indeed, the action potentials carried into the nervous system by a sensory axon often are indistinguishable from those carried out of the nervous system to the muscles by a motor axon.

Only two features of the conducting signal convey information: the number of action potentials and the time intervals between them (Figure 2–10C). As Adrian put it in 1928, summarizing his work on sensory fibers: "all impulses are very much alike, whether the message is destined to arouse the sensation of light, of touch, or of pain; if they are crowded together the sensation is intense, if they are separated by long intervals the sensation is correspondingly feeble." Thus, what determines the intensity of sensation or speed of movement is the frequency of the action potentials. Likewise, the duration of a sensation or movement is determined by the period over which action potentials are generated.

In addition to the frequency of the action potentials, the pattern of action potentials also conveys important information. For example, some neurons are not silent in the absence of stimulation but are spontaneously active. Some spontaneously active nerve cells (beating neurons) fire action potentials regularly; other neurons (bursting neurons) fire in brief bursts of action potentials. These diverse cells respond differently to the same excitatory synaptic input. An excitatory synaptic potential may initiate one or more action potentials in a cell that does not have a spontaneous activity, but in spontaneously active cells that same input will modulate the rhythm by increasing the rate of firing of action potentials.

An even more dramatic difference is seen when the input signal is inhibitory. Inhibitory inputs have little information value in a silent cell. By contrast, in spontaneously active cells inhibition can have a powerful *sculpting* role. By establishing periods of silence in otherwise ongoing activity, inhibition can produce a complex pattern of alternating firing and silence where none existed. These subtle differences in firing patterns may have important functional consequences for the information transfer between neurons. This has led mathematical modelers of neuronal networks to attempt to delineate neural codes in which information is also carried by the fine-grained pattern of firing—the exact timing of action potentials (Figure 2–11).

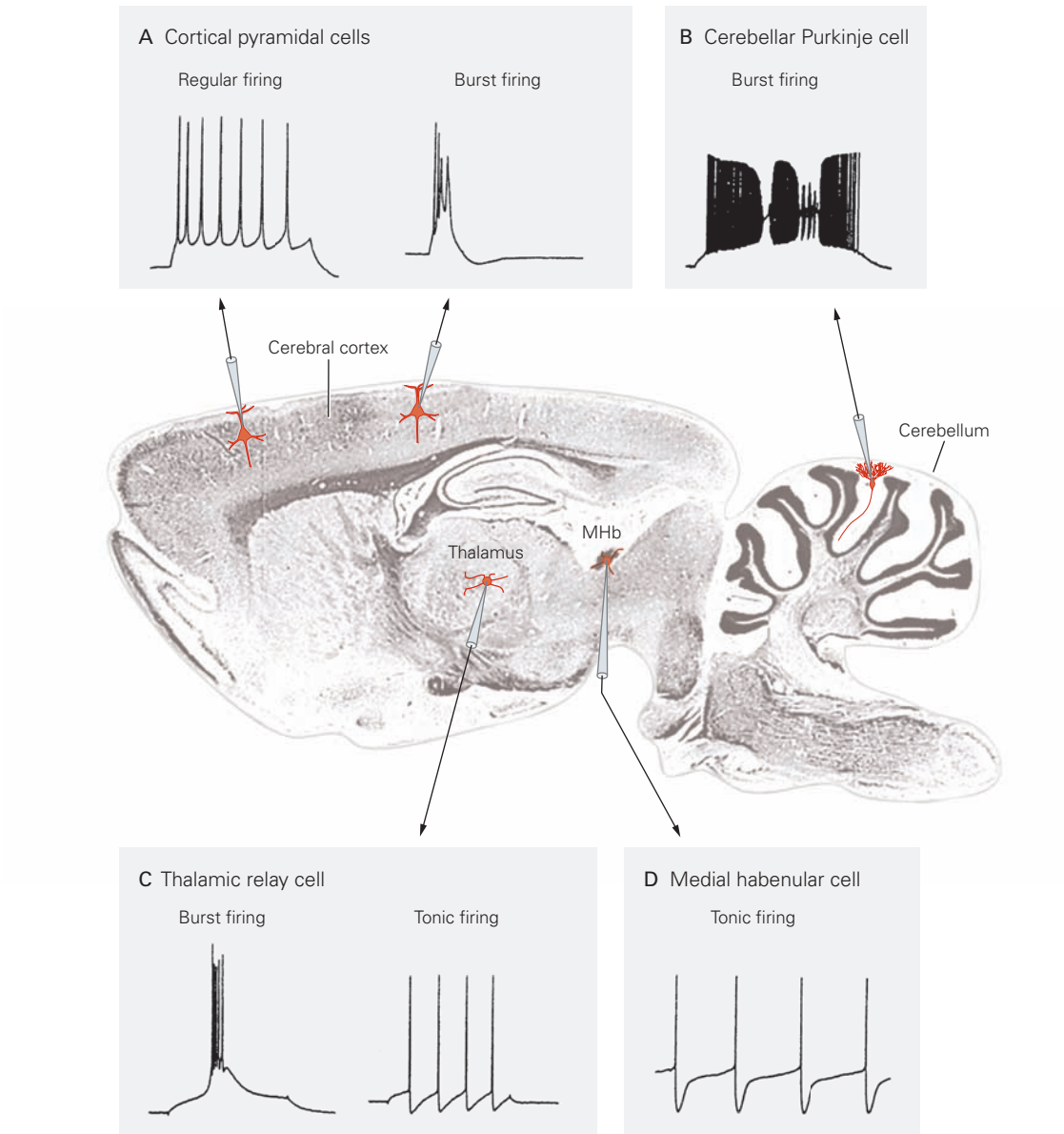

Figure 2–11 Neurons in the mammalian brain exhibit widely varying electrophysiological properties. (Reproduced, with permission, from McCormick, 2004.)

A. Intracellular injection of a depolarizing current pulse in a cortical pyramidal cell results in a train of action potentials that decline in frequency. This pattern of activity is known as regular firing. Some cortical cells generated bursts of three or more action potentials, even when depolarized only for a short period.

B. Cerebellar Purkinje cells generate high-frequency trains of action potentials in their cell bodies that are disrupted by the generation of Ca^{2+} action potentials in their dendrites. These cells can also generate plateau potentials from the persistent activation of Na^{+} conductances.

C. Thalamic relay cells may generate action potentials either as bursts or tonic trains of action potentials owing to the presence of a large low-threshold Ca^{2+} current.

D. Medial habenular cells generate action potentials at a steady and slow rate, in a pacemaker fashion.

If signals are stereotyped and reflect only the most elementary properties of the stimulus, how can they carry the rich variety of information needed for complex behavior? How is a message that carries visual information about a bee distinguished from one that carries pain information about the bee's sting, and how are these sensory signals distinguished from motor signals for voluntary movement? The answer is simple and yet is one of the most important organizational principles of the nervous system: Pathways of connected neurons, not individual neurons, convey information. Interconnected neurons form anatomically and functionally distinct pathways. The neural pathways activated by receptor cells in the retina that respond to light are completely distinct from the pathways activated by sensory cells in the skin that respond to touch.

The Output Component Releases Neurotransmitter

When an action potential reaches a neuron's terminal it stimulates the release of chemical substances from the cell. These substances, called *neurotransmitters,* can be small organic molecules, such as L-glutamate and acetylcholine, or peptides like substance P or LHRH (luteinizing hormone releasing hormone).

Neurotransmitter molecules are held in subcellular organelles called *synaptic vesicles,* which accumulate at specialized release sites in the terminals of the axon called *active zones.* To eject their transmitter substance into the synaptic cleft, the vesicles move up to and fuse with the neuron's plasma membrane, then burst open, a process known as *exocytosis.* The molecular machinery of neurotransmitter release is described in Chapters 11 and 12.

Once released, the neurotransmitter is the neuron's output signal. Like the input signal, it is graded. The amount of transmitter released is determined by the number and frequency of the action potentials that reach the presynaptic terminals (Figure 2–10C,D). After release the transmitter diffuses across the synaptic cleft and binds to receptors on the postsynaptic neuron. This binding causes the postsynaptic cell to generate a synaptic potential. Whether the synaptic potential has an excitatory or inhibitory effect depends on the type of receptor in the postsynaptic cell, not on the particular chemical neurotransmitter. The same transmitter substance can have different effects at different receptors.

The Transformation of the Neural Signal from Sensory to Motor Is Illustrated by the Stretch-Reflex Pathway

We have seen that the properties of a signal are transformed as the signal moves from one component of a neuron to another or between neurons. This transformative chain of events can be seen in the relay of signals for the stretch reflex.

When a muscle is stretched, the amplitude and duration of the stimulus are reflected in the amplitude and duration of the receptor potential generated in the sensory neuron (Figure 2–12A). If the receptor potential exceeds the threshold for an action potential in that cell, the graded signal is transformed at the trigger zone into an action potential, an all-or-none signal. The more the receptor potential exceeds threshold, the greater the depolarization and consequently the greater the frequency of action potentials in the axon. The duration of the input signal also determines the duration of the train of action potentials.

The information encoded by the frequency and duration of firing is faithfully conveyed along the axon to its terminals, where the firing of action potentials determines the amount of transmitter released. These stages of signaling have their counterparts in the motor neuron (Figure 2–12B) and in the muscle (Figure 2–12C).

Nerve Cells Differ Most at the Molecular Level

The model of neuronal signaling we have outlined is a simplification that applies to most neurons but there are some important variations. For example, some neurons do not generate action potentials. These are typically local interneurons without a conductive component; they have no axon or such a short one that regeneration of the signal is not required. In these neurons the input signals are summed and spread passively to the presynaptic terminal region nearby where transmitter is released. Neurons that are spontaneously active do not require sensory or synaptic inputs to fire action potentials because they have a special class of ion channels that permit Na^+ current flow even in the absence of excitatory synaptic input.

Even cells that are similar morphologically can differ importantly in molecular details. For example, they can have different combinations of ion channels. As we shall learn in Chapter 7, different ion channels provide neurons with various thresholds, excitability properties, and firing patterns (Figure 2–11). Neurons with different ion channels can therefore encode synaptic potentials into different firing patterns and thereby convey different information.

Neurons also differ in the chemical substances they use as transmitters and in the receptors that receive transmitter substances from other neurons. Indeed, many drugs that act on the brain do so by modifying the actions of specific chemical transmitters or receptors.

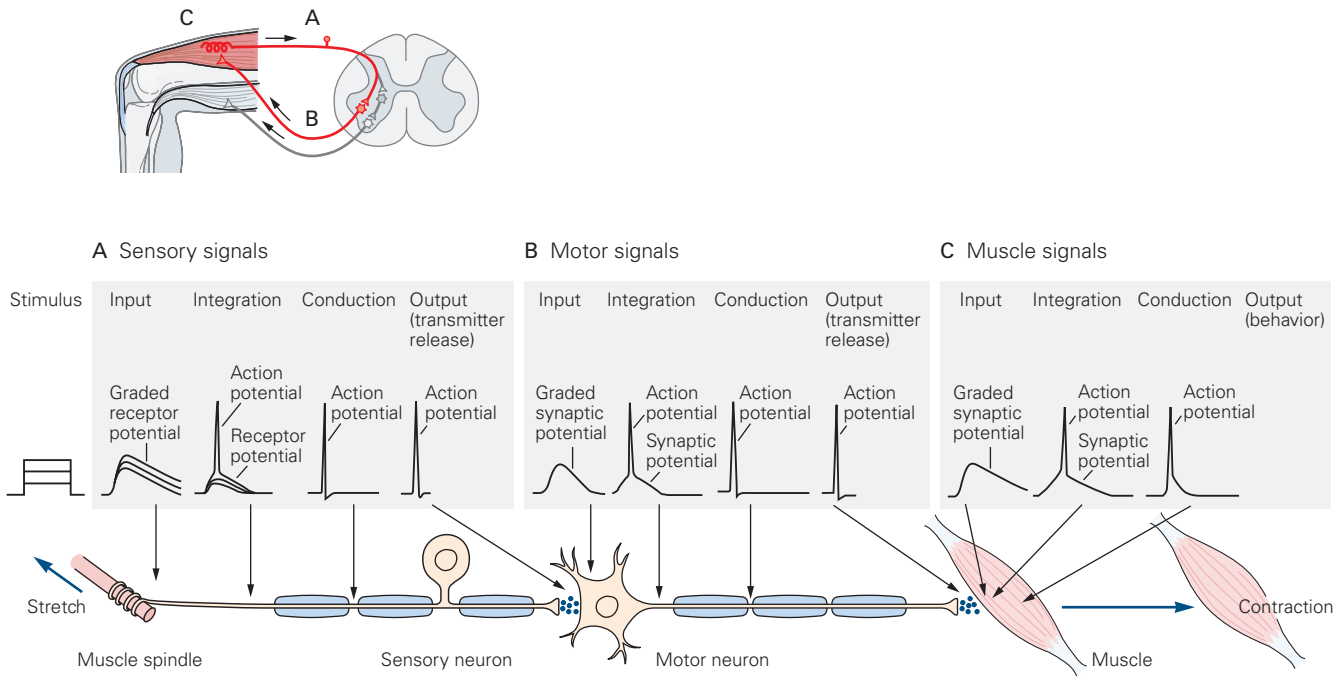

Figure 2–12. The sequence of signals that produces a reflex action.

A. The stretching of a muscle produces a receptor potential in the specialized receptor (the muscle spindle). The amplitude of the receptor potential is proportional to the intensity of the stretch. This potential spreads passively to the integrative or trigger zone at the first node of Ranvier. If the receptor potential is sufficiently large, it triggers an action potential that then propagates actively and without change along the axon to the axon terminal. At specialized sites in the terminal the action potential leads to an output signal, the release of a chemical neurotransmitter. The transmitter diffuses across the synaptic cleft between the axon terminal and a target motor neuron that innervates the stretched muscle; it then binds to receptor molecules on the external membrane of the motor neuron.

B. This interaction initiates a synaptic potential that spreads passively to the trigger zone of the motor neuron's axon, where it initiates an action potential that propagates actively to the terminal of the motor neuron's axon. The action potential releases a neuro transmitter where the axon terminal meets a muscle fiber.

C. The neurotransmitter binds receptors on the muscle fiber, triggering a synaptic potential in the muscle. If sufficiently large, or if combined with signals from other motor neurons, the synaptic potential will generate an action potential in the muscle, causing contraction of the muscle fiber.

Because of physiological differences among neurons, a disease may affect one class of neurons but not others. Certain diseases strike only motor neurons (amyotrophic lateral sclerosis and poliomyelitis), whereas others affect primarily sensory neurons (tabes dorsalis, a late stage of syphilis). Parkinson disease, a disorder of voluntary movement, damages a small population of interneurons that use dopamine as a neurotransmitter. Some diseases are selective even within the neuron, affecting only the receptive elements, the cell body, or the axon. In Chapter 14 we describe how research into myasthenia gravis, a disease caused by a faulty transmitter receptor in the muscle membrane, has provided important insights into synaptic transmission. Indeed, because the nervous system has so many cell types and variations at the molecular level, it is susceptible to more diseases (psychiatric as well as neurological) than any other organ system of the body.

Despite the differences among nerve cells, the basic mechanisms of electrical signaling are surprisingly similar. This simplicity is fortunate, for understanding the molecular mechanisms of signaling in one kind of nerve cell aids the understanding of these mechanisms in many other nerve cells.

Neural Network Models Simulate the Brain's Parallel Processing of Information

The stretch reflex illustrates how interactions between just a few types of nerve cells can constitute a functional circuit that produces a simple behavior, even

though the number of neurons involved is large (the stretch reflex circuit has perhaps a few hundred sensory neurons and a hundred motor neurons). Can the individual neurons implicated in a complex behavior be identified with the same precision?

In invertebrate animals, and in some lower-order vertebrates, a single cell (a so-called command cell) can initiate a complex behavioral sequence. But as far as we know no complex human behavior is initiated by a single neuron. Rather, each behavior is generated by the actions of many cells. Broadly speaking, as we have seen, there are three components of the neural control of behavior: sensory input, intermediate processing, and motor output. In vertebrates each component is likely to be mediated by a single group or several distinct groups of neurons.

Moreover, each component may have multiple neural pathways that simultaneously provide the same or similar information. The deployment of several neuronal groups or pathways to convey similar information is called *parallel processing*. Parallel processing also occurs in a single pathway when different neurons in the pathway perform similar computations simultaneously. Parallel processing makes enormous sense as an evolutionary strategy for building a more powerful brain, for it increases both the speed and reliability of function within the central nervous system.

The importance of abundant, highly specific parallel connections has long been recognized by scientists attempting to construct theoretical models of the brain. The branch of computer science known as artificial intelligence originally used serial processing to simulate the brain's cognitive processes—pattern recognition, learning, memory, and motor performance. These serial models performed many tasks rather well, including playing chess. However, they performed poorly with other computations that the brain does almost instantaneously, such as recognizing faces or comprehending speech.

Many theoretical neurobiologists have turned to different types of models that include parallel processing, which they call *neural networks.* In these models, elements of the system process information simultaneously using both feed-forward and feedback connections. Interestingly, in systems with feedback circuits it is the dynamic activity of the system that determines the outcome of computation, not inputs or initial conditions.

Neural network models capture well the highly recurrent architecture of most actual neural circuits and also the ability of the brain to function in the absence of specific sensory input from outside the body such as during thinking, sleep, and the generation of endogenous rhythms, something with which traditional deterministic models have difficulty. Neural network models also show that analysis of individual elements of a system may not be enough to decode the *action potential code.* According to this neural network view, what makes the brain a remarkable information processing organ is not the complexity of its neurons but the fact that it has many elements interconnected in a variety of complex ways. Neural network modeling is discussed in Appendices E and F.

Neural Connections Can Be Modified by Experience

Most learning results in behavioral changes that endure for years, but even simple reflexes can be modified briefly. The fact that behavior is learned raises an interesting question: How is behavior modified if the nervous system is wired so precisely? How can changes in the neural control of behavior occur when connections between the signaling units, the neurons, are set during early development?

Several solutions for this dilemma have been proposed. The proposal that has proven most farsighted is the *plasticity hypothesis,* first put forward at the turn of the 20th century by Ramón y Cajal. A modern form of this hypothesis was advanced by the Polish psychologist Jerzy Konorski in 1948:

> The application of a stimulus leads to changes of a twofold kind in the nervous system . . . [T]he first property, by virtue of which the nerve cells *react* to the incoming impulse . . . we call *excitability,* and . . . changes arising . . . because of this property we shall call *changes due to excitability*. The second property, by virtue of which certain permanent functional transformations arise in particular systems of neurons as a result of appropriate stimuli or their combination, we shall call *plasticity* and the corresponding changes *plastic changes*.

There is now considerable evidence for functional plasticity at chemical synapses. These synapses often have a remarkable capacity for short-term physiological changes (lasting seconds to hours) that increase or decrease synaptic effectiveness. Long-term changes (lasting days) can give rise to further physiological changes that lead to anatomical alterations, including pruning of preexisting synapses and even growth of new ones.

As we shall see in later chapters, chemical synapses are functionally and anatomically modified through experience and learning as much as during early development. Functional alterations, physiological changes, are typically short-term and result in changes in the effectiveness of existing synaptic connections.

Anatomical alterations are typically long-term and consist of the growth of new synaptic connections between neurons. It is this functional plasticity of neurons that endows each of us with our individuality.

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Ben A. Barres
A. J. Hudspeth

Selected Readings

Adrian ED. 1928. *The Basis of Sensation: The Action of the Sense Organs.* London: Christophers.

Gazzaniga MS (ed). 1995. *The Cognitive Neurosciences.* Cambridge, MA: MIT Press.

Jones EG. 1988. The nervous tissue. In: L Weiss (ed). *Cell and Tissue Biology: A Textbook of Histology,* 6th ed., pp. 277–351. Baltimore: Urban and Schwarzenberg.

Newan EA. 1993. Inward-rectifying potassium channels in retinal glial (Muller) cells. J Neurosci 13:3333–3345.

Perry VH. 1996. Microglia in the developing and mature central nervous system. In: KR Jessen, WD Richardson (eds). *Glial Cell Development: Basic Principles & Clinical Relevance,* pp. 123–140. Oxford: Bios.

Ramón y Cajal S. 1937. *1852–1937. Recollections of My Life.* EH Craigie (transl). Philadelphia: American Philosophical Society; 1989. Reprint. Cambridge, MA: MIT Press.

References

Adrian ED. 1932. *The Mechanism of Nervous Action: Electrical Studies of the Neurone.* Philadelphia: Univ. Pennsylvania Press.

Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter JD. 2002. *Molecular Biology of the Cell,* 4th ed. New York: Garland.

Dacey DM, Peterson BB, Robinson FR, Gamlin PD. 2003. Fireworks in the primate retina: in vitro photodynamics reveals diverse LGN-projecting ganglion cell types. Neuron 37:15–27.

Erlanger J, Gasser HS. 1937. *Electrical Signs of Nervous Activity.* Philadelphia: Univ. Pennsylvania Press.

Hodgkin AL, Huxley AF. 1939. Action potentials recorded from inside a nerve fiber. Nature 144:710–711.

Hopfield JJ, Tank DW. 1986. Computing with neural circuits: a model. Science 233:625–633.

Kandel ER. 1976. The study of behavior: the interface between psychology and biology. In: *Cellular Basis of Behavior: An Introduction to Behavioral Neurobiology,* pp. 3–27. San Francisco: WH Freeman.

Konorski J. 1948. *Conditioned Reflexes and Neuron Organization.* Cambridge, MA: Cambridge Univ. Press.

Martinez PFA. 1982. *Neuroanatomy: Development and Structure of the Central Nervous System.* Philadelphia: Saunders.

McCormick DA. 2004. Membrane potential and action potential. In: JH Byrne and JL Roberts (eds.) *From Molecules to Networks: An Introduction to Cellular Neuroscience*, 2nd ed., p. 130. San Diego, CA: Elsevier.

Newman EA. 1986. High potassium conductance in astrocyte endfeet. Science 233:453–454.

Nicholls JG, Wallace BG, Fuchs PA, Martin AR. 2001. *From Neuron to Brain,* 4th ed. Sunderland, MA: Sinauer.

Penfield W (ed). 1932. *Cytology & Cellular Pathology of the Nervous System,* Vol. 2. New York: Hoeber.

Ramón y Cajal S. 1933. *Histology,* 10th ed. Baltimore: Wood.

Sears ES, Franklin GM. 1980. Diseases of the cranial nerves. In: RN Rosenberg (ed). *The Science and Practice of Clinical Medicine.* Vol. 5, *Neurology,* pp. 471–494. New York: Grune & Stratton.

Sherrington C. 1947. *The Integrative Action of the Nervous System,* 2nd ed. Cambridge, MA: Cambridge Univ. Press.