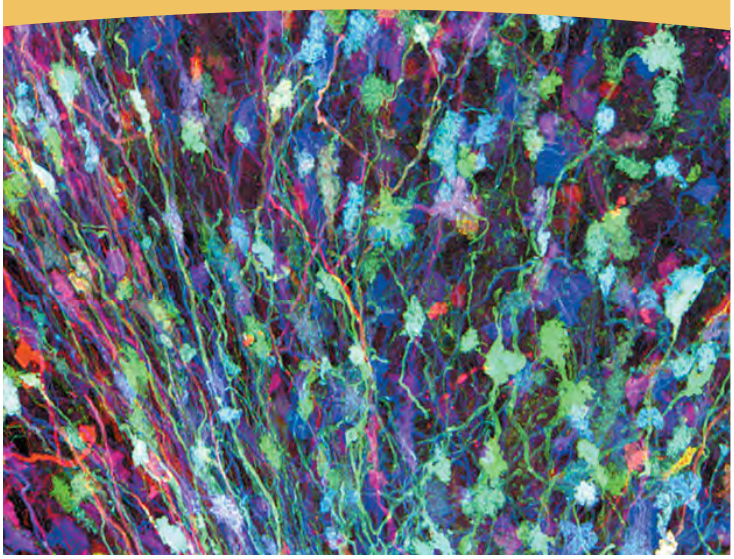
49

Nervous Systems



▲ **Figure 49.1 How do scientists identify individual neurons in the brain?**

KEY CONCEPTS

OVERVIEW

Command and Control Center

What happens in your brain when you solve a math problem or listen to music? Until quite recently, scientists had little hope of answering that question. The human brain contains an estimated 10^{11} (100 billion) neurons. Interconnecting these brain cells are circuits more complex than those of even the most powerful supercomputers. Yet the circuitry of the brain has been largely hidden from view. That's no longer the case, thanks in part to several exciting new technologies.

One recent advance in exploring the brain relies on a method for expressing random combinations of colored proteins in brain cells—such that each cell shows up in a different color. The result is a "brainbow" like the one in **Figure 49.1**, which highlights neurons in the brain of a mouse. In this image, each neuron expresses one of more than 90 different color combinations of four fluorescent proteins. Using the brainbow technology, neuroscientists hope to develop detailed maps of the connections that transfer information between particular regions of the brain.

Another breakthrough came with the development of powerful imaging techniques that reveal activity in the working brain. Researchers can monitor multiple areas of the human brain while a subject is performing various tasks, such as speaking, looking at pictures, or forming a mental image of a person's face. They can use these techniques to look for a correlation between a particular task and activity in specific brain areas.

In this chapter, we will discuss the organization and evolution of animal nervous systems, exploring how groups of neurons function in specialized circuits dedicated to specific tasks. First we'll focus on specialization in regions of the vertebrate brain. We will then turn to the ways in which brain activity makes information storage and organization possible. Finally, we'll consider several disorders of the nervous system that are the subject of intense research today.

CONCEPT **49.1**

Nervous systems consist of circuits of neurons and supporting cells

The ability to sense and react originated billions of years ago with prokaryotes that could detect changes in their environment and respond in ways that enhanced their survival and reproductive success. For example, bacteria keep moving in a particular direction as long as they encounter increasing concentrations of a food source. Later in evolution, modification of simple recognition and response processes provided multicellular organisms with a mechanism for communication between cells of the body. By the time of the Cambrian explosion more than 500 million years ago (see Chapter 32), systems of neurons allowing animals to sense and move rapidly were present in essentially their current forms.

Hydras, jellies, and other cnidarians are the simplest animals with nervous systems. As you read in Chapters 33 and 41, these animals have radially symmetrical bodies organized around a central digestive compartment, the gastrovascular cavity. In most cnidarians, interconnected nerve cells form a

diffuse **nerve net** (Figure 49.2a), which controls the contraction and expansion of the gastrovascular cavity. Unlike the nervous systems of other animals, the nerve net of cnidarians lacks clusters of neurons that perform specialized functions.

In more complex animals, the axons of multiple nerve cells are often bundled together, forming **nerves**. These fibrous structures channel and organize information flow along specific routes through the nervous system. For example, sea stars have a set of radial nerves connecting to a central nerve ring (Figure 49.2b). Within each arm of a sea star, the radial nerve is linked to a nerve net from which it receives input and to which it sends signals controlling muscle contraction.

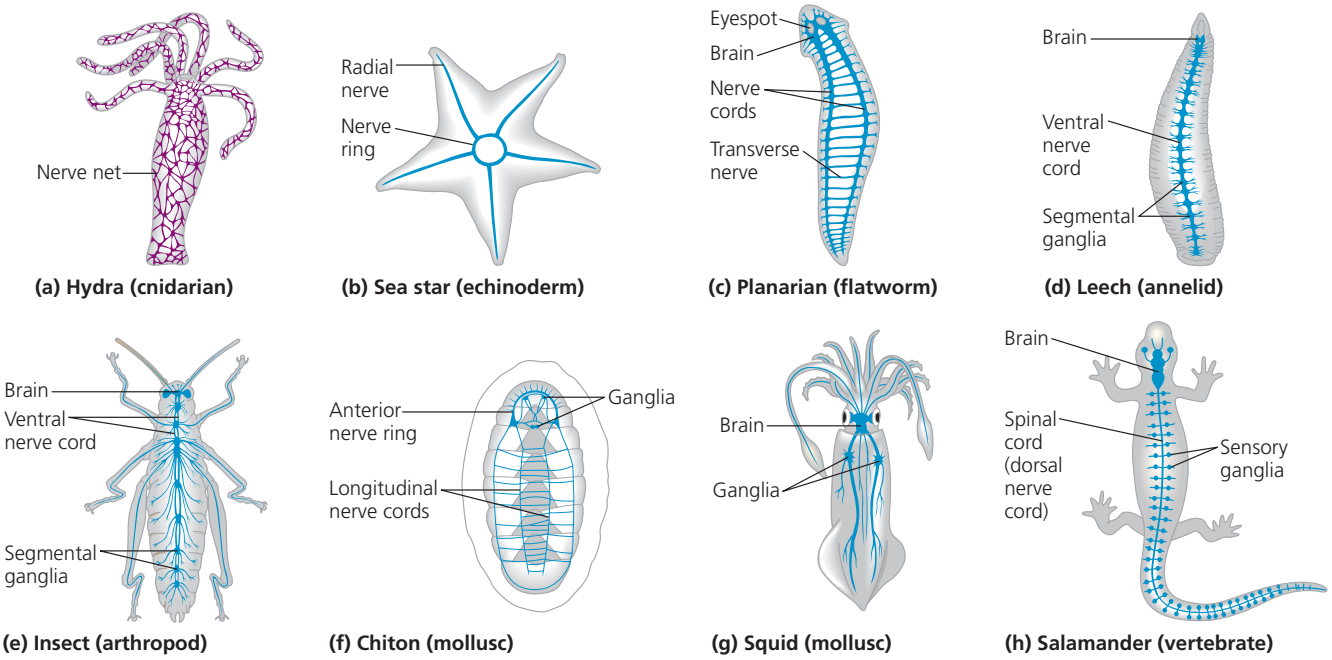
Animals that have elongated, bilaterally symmetrical bodies have even more specialized nervous systems. Such animals exhibit cephalization, an evolutionary trend toward a clustering of sensory neurons and interneurons at the anterior (front) end of the body. These anterior neurons communicate with cells elsewhere in the body, including neurons located in one or more nerve cords extending toward the posterior (rear) end. In nonsegmented worms, such as the planarian shown in Figure 49.2c, a small brain and longitudinal nerve cords constitute the simplest clearly defined *central nervous system* (*CNS*). In some such animals, the entire nervous system is constructed from only a small number of cells, as shown by studies of another nonsegmented worm, the nematode *Caenorhabditis elegans*. In this species, an adult worm (hermaphrodite) has exactly 302 neurons, no more and no fewer. More complex invertebrates, such as segmented worms (annelids; Figure 49.2d) and arthropods (Figure 49.2e), have many more neurons. The behavior of such invertebrates is regulated by more complicated brains and by ventral nerve cords containing ganglia, segmentally arranged clusters of neurons.

Within an animal group, nervous system organization often correlates with lifestyle. Among the molluscs, for example, sessile and slow-moving species, such as clams and chitons, have relatively simple sense organs and little or no cephalization (Figure 49.2f). In contrast, active predatory molluscs, such as octopuses and squids (Figure 49.2g), have the most sophisticated nervous systems of any invertebrates, rivaling those of some vertebrates. With their large, image-forming eyes and a brain containing millions of neurons, octopuses can learn to discriminate between visual patterns and to perform complex tasks.

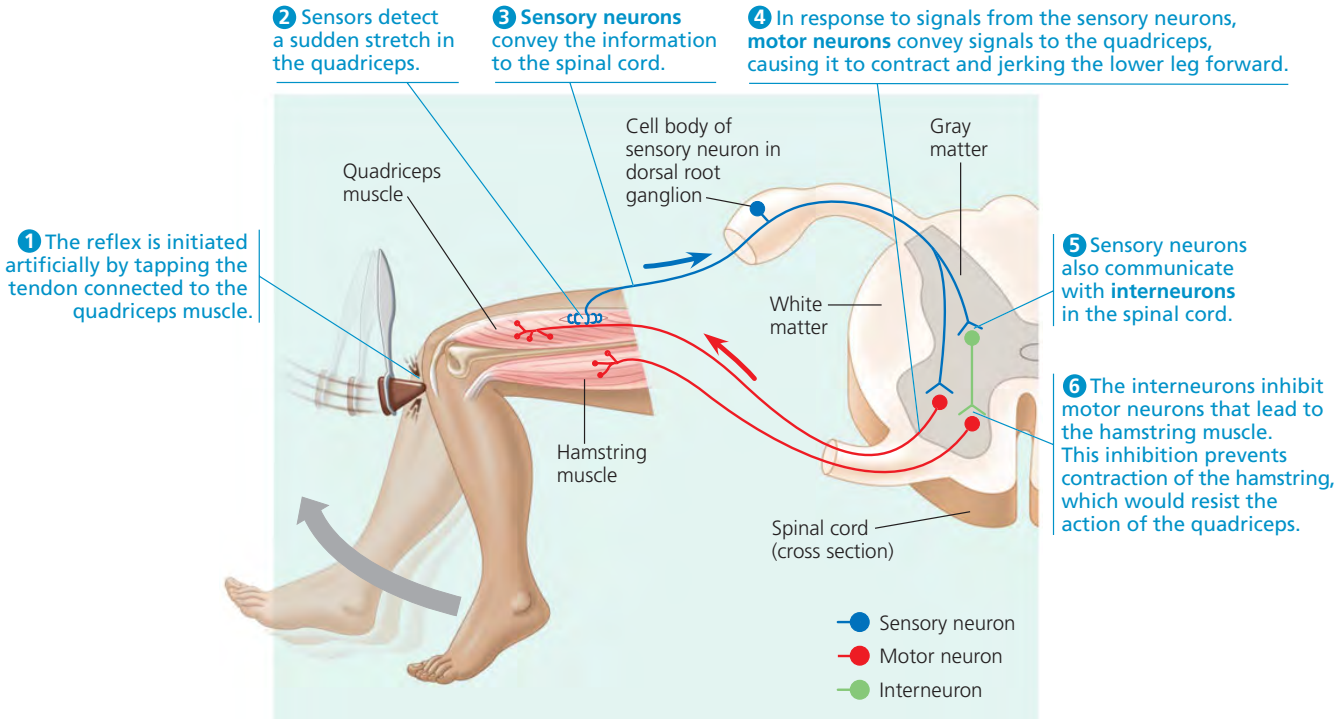
In vertebrates (Figure 49.2h), the brain and the spinal cord form the CNS; nerves and ganglia form the *peripheral nervous system* (*PNS*). Regional specialization is a hallmark of both systems, as we will see throughout the remainder of this chapter.

Organization of the Vertebrate Nervous System

In the vertebrate CNS, the functions of the brain and spinal cord are tightly coordinated. The brain provides the integrative power that underlies the complex behavior of vertebrates. The spinal cord, which runs lengthwise inside the vertebral column (spine), conveys information to and from the brain



▲ **Figure 49.2 Nervous system organization. (a)** A hydra contains individual neurons (purple) organized in a diffuse nerve net. **(b–h)** Animals with more sophisticated nervous systems contain groups of neurons (blue) organized into nerves and often ganglia and a brain.



▲ **Figure 49.3 The knee-jerk reflex.** Many neurons are involved in the reflex, but for simplicity, only a few neurons are shown.

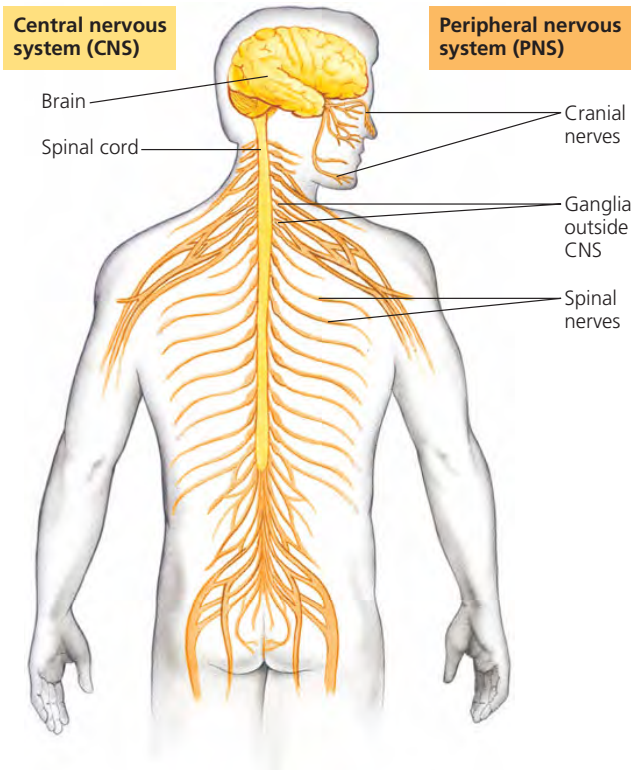
MAKE CONNECTIONS *Using the nerve signals to the hamstring and quadriceps in this reflex as an example, propose a model for regulation of smooth muscle activity in the esophagus during the swallowing reflex (see Figure 41.10, p. 884).*

and generates basic patterns of locomotion. The spinal cord also acts independently of the brain as part of the simple nerve circuits that produce **reflexes**, the body's automatic responses to certain stimuli.

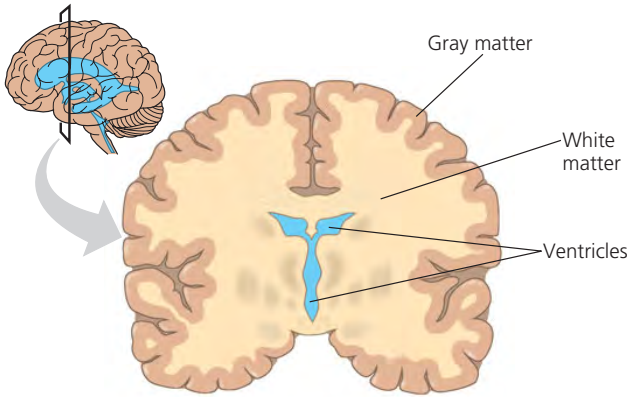
A reflex protects the body by triggering a rapid, involuntary response to a particular stimulus. If you put your hand on a hot burner, a reflex begins to pull your hand back well before the sensation of pain has been processed in your brain. Similarly, if your knees buckle when you pick up a heavy object, the tension across your knees triggers a reflex that contracts the thigh muscles, helping you stay upright and support the load. During a physical exam, your doctor may trigger this knee-jerk reflex with a mallet to help assess nervous system function **(Figure 49.3)**.

Whereas the nerve cord of many invertebrates is located ventrally, the spinal cord of vertebrates runs along the dorsal side of the body **(Figure 49.4)**. An underlying segmental organization is apparent in the arrangement of neurons within the spinal cord and in the distribution of spinal nerves and ganglia just outside the spinal cord.

During embryonic development in vertebrates, the central nervous system develops from the hollow dorsal nerve cord—a hallmark of chordates (see Chapter 34). The cavity



▲ **Figure 49.4 The vertebrate nervous system.** The central nervous system consists of the brain and spinal cord (yellow). Left-right pairs of cranial nerves, spinal nerves, and ganglia make up most of the peripheral nervous system (dark gold).



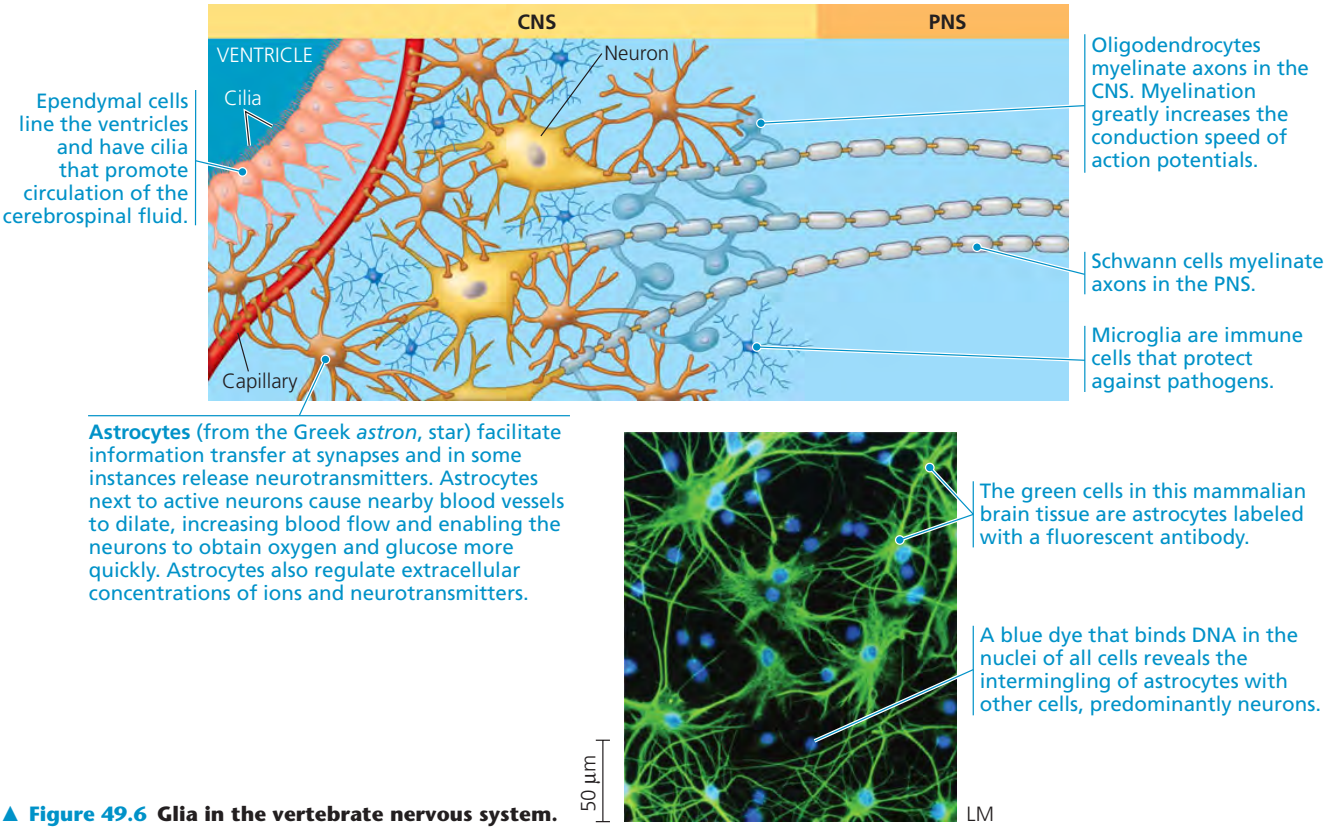
▲ **Figure 49.5 Ventricles, gray matter, and white matter.** Ventricles deep in the brain's interior contain cerebrospinal fluid. Most of the gray matter is on the surface of the brain, surrounding the white matter.

of the nerve cord gives rise to the narrow **central canal** of the spinal cord as well as the **ventricles** of the brain **(Figure 49.5)**. Both the canal and ventricles fill with **cerebrospinal fluid**, which is formed in the brain by filtration of arterial blood. The cerebrospinal fluid circulates slowly through the central canal and ventricles and then drains into the veins. This circulation supplies the brain with nutrients and hormones and carries away wastes. In mammals, the cerebrospinal fluid also cushions the brain and spinal cord by circulating between layers of connective tissue that surround the CNS.

In addition to these fluid-filled spaces, the brain and spinal cord contain gray matter and white matter (see Figure 49.5). **Gray matter** consists mainly of neuron cell bodies, dendrites, and unmyelinated axons. In contrast, **white matter** consists of bundled axons that have myelin sheaths, which give the axons a whitish appearance. White matter in the spinal cord lies on the outside, consistent with its function in linking the CNS to sensory and motor neurons of the PNS. White matter in the brain is predominantly on the inside, reflecting the role of signaling between neurons of the brain in learning, feeling emotions, processing sensory information, and generating commands.

Glia

The glia present throughout the vertebrate brain and spinal cord carry out functions crucial for the activity of the nervous system. **Figure 49.6** illustrates the major types of glia in the adult nervous system and provides an overview of the ways in which they nourish, support, and regulate the functioning of neurons.



▲ **Figure 49.6 Glia in the vertebrate nervous system.**

Glia also have an essential role in development of the nervous system. In embryos, cells called *radial glia* form tracks along which newly formed neurons migrate from the neural tube, the structure that gives rise to the CNS (see Figure 47.13). Later, astrocytes induce cells that line the capillaries in the CNS to form tight junctions (see Figure 6.32). The result is the *blood-brain barrier*, which controls the extracellular environment of the CNS by restricting the entry of most substances from the blood.

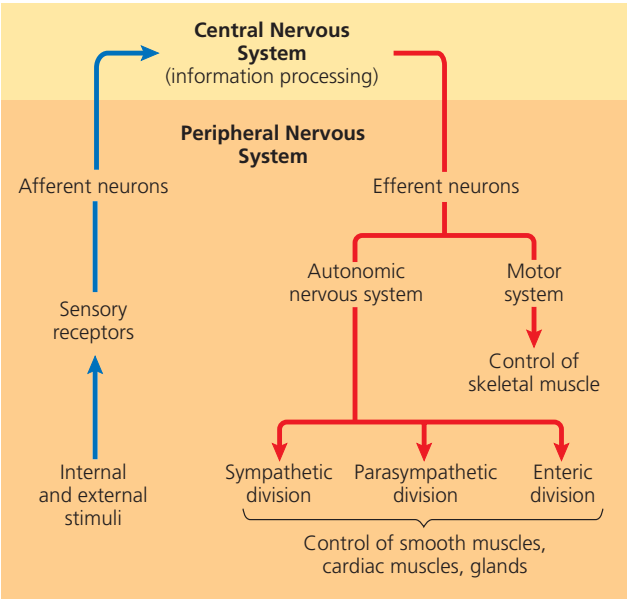
Both radial glia and astrocytes can also act as stem cells, generating new neurons and glia. Researchers view these multipotent precursors as a potential means for replacing neurons and glia that are lost to injury or disease, a topic we'll explore further in Concept 49.4.

The Peripheral Nervous System

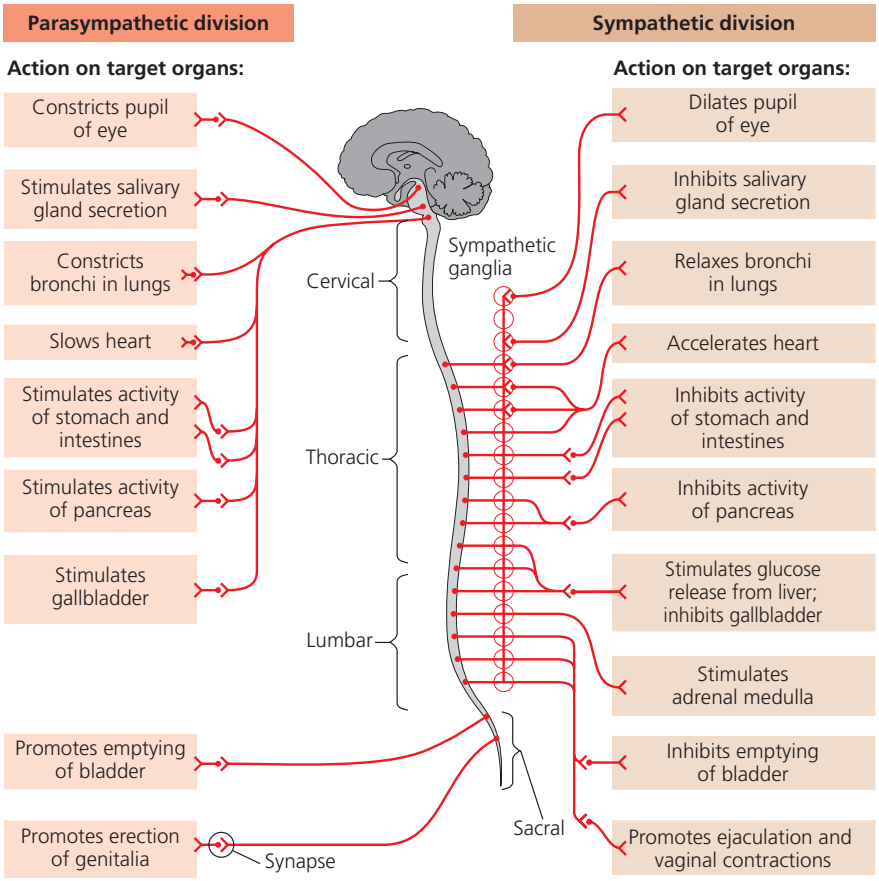
The PNS transmits information to and from the CNS and plays a large role in regulating an animal's movement and internal environment **(Figure 49.7)**. Sensory information reaches the CNS along PNS neurons designated as *afferent* (from the Latin, meaning "to carry toward"). Following information processing within the CNS, instructions then travel to muscles, glands, and endocrine cells along PNS neurons designated as *efferent* (from the Latin, meaning "to carry away"). Most nerves contain both afferent and efferent neurons. One exception is the olfactory nerve, which conveys only sensory information from the nose to the brain.

The PNS has two efferent components: the motor system and the autonomic nervous system (see Figure 49.7). The **motor system** consists of neurons that carry signals to skeletal muscles. This control of skeletal muscles can be voluntary, as when you raise your hand to ask a question, or involuntary, as in the knee-jerk reflex controlled by the spinal cord. In contrast, regulation of smooth and cardiac muscles by the **autonomic nervous system** is generally involuntary. The three divisions of the autonomic nervous system—sympathetic, parasympathetic, and enteric—together control the organs of the digestive, cardiovascular, excretory, and endocrine systems.

The sympathetic and parasympathetic divisions of the autonomic nervous system have largely antagonistic (opposite) functions in regulating organ function **(Figure 49.8)**. Activation of



▲ **Figure 49.7 Functional hierarchy of the vertebrate peripheral nervous system.**



▲ **Figure 49.8 The parasympathetic and sympathetic divisions of the autonomic nervous system.** Most pathways in each division consist of preganglionic neurons (having cell bodies in the CNS) and postganglionic neurons (having cell bodies in ganglia in the PNS).

the **sympathetic division** corresponds to arousal and energy generation (the "fight-or-flight" response). For example, the heart beats faster, digestion is inhibited, the liver converts glycogen to glucose, and the adrenal medulla increases secretion of epinephrine (adrenaline) and norepinephrine. Activation of the **parasympathetic division** generally causes opposite responses that promote calming and a return to self-maintenance functions ("rest and digest"). Thus, heart rate decreases, digestion is enhanced, and glycogen production increases. In regulating reproductive activity, however, the parasympathetic division complements rather than antagonizes the sympathetic division (see Figure 49.8).

Networks of neurons that form the **enteric division** of the PNS are active in the digestive tract, pancreas, and gallbladder. Within these organs, the enteric division regulates secretion and peristalsis (see Chapter 41). The sympathetic and parasympathetic divisions normally regulate the enteric division, although it is capable of independent activity.

Homeostasis often relies on cooperation between the motor and autonomic nervous systems. In response to a drop in body temperature, for example, the hypothalamus signals the motor system to cause shivering, which increases heat production. At the same time, the hypothalamus signals the autonomic nervous system to constrict surface blood vessels, reducing heat loss.

CONCEPT CHECK 49.1

1. Which division of the autonomic nervous system would likely be activated if a student learned that an exam she had forgotten about would start in 5 minutes? Explain your answer.
2. The parasympathetic and sympathetic divisions of the PNS (see Figure 49.8) use the same neurotransmitters at the axon terminals of preganglionic neurons, but different neurotransmitters at the axon terminals of postganglionic neurons. How does this difference correlate with the function of the axons bringing signals into and out of the ganglia in the two divisions?
3. **WHAT IF?** Suppose a person had an accident that severed a small nerve required to move some of the fingers of the right hand. Would you also expect an effect on sensation from those fingers?
4. **MAKE CONNECTIONS** Most tissues regulated by the autonomic nervous system receive both sympathetic and parasympathetic input from postganglionic neurons. Responses are typically local. In contrast, the adrenal medulla receives input only from the sympathetic division and only from preganglionic neurons, yet responses are observed throughout the body. Explain why (see Figure 45.21, p. 991).

For suggested answers, see Appendix A.

CONCEPT 49.2

The vertebrate brain is regionally specialized

Having considered some of the basic functions of the PNS, we turn now to the brain. Images of the human brain in popular culture almost always focus on the cerebrum, the part of the brain whose surface lies just beneath the skull. The cerebrum is responsible for many activities we commonly associate with the brain, such as calculation, contemplation, and memory. Underneath the cerebrum, however, are additional brain structures with important and diverse activities, including homeostasis, coordination, and information transfer.

Figure 49.9, on pages 1068–1069, explores the origin, form, and function of major regions of the human brain. It outlines how brain structures arise during embryonic development, illustrates their size, shape, and location in the adult, and summarizes their best-understood functions. Figure 49.9 will serve as an introduction to the regional specialization in the brain and provide a useful point of reference for later discussions of specific brain functions.

To learn more about how brain organization relates to brain function, we'll first consider activity cycles of the brain and the physiological basis of emotion. Then, in Concept 49.3, we'll shift our attention to regional specialization within the cerebrum.

Arousal and Sleep

If you've ever drifted off to sleep while listening to a lecture (or reading a book), you know that your attentiveness and mental alertness can change rapidly. Such transitions are regulated by the brainstem and cerebrum, which control arousal and sleep. Arousal is a state of awareness of the external world. Sleep is a state in which external stimuli are received but not consciously perceived.

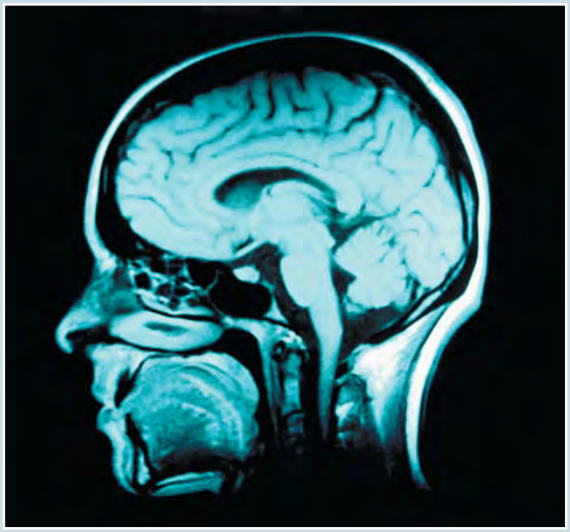
Contrary to appearances, sleep is an active state, at least for the brain. By placing electrodes at multiple sites on the scalp, we can record patterns of electrical activity called brain waves in an electroencephalogram (EEG). These recordings reveal that brain wave frequencies change as the brain progresses through distinct stages of sleep.

Although sleep is essential for survival, we still know very little about its function. One hypothesis is that sleep and dreams are involved in consolidating learning and memory. This hypothesis is supported by the finding that test subjects who are kept awake for 36 hours have a reduced ability to remember when particular events occurred, even if they first "perk up" with caffeine. Other experiments show that regions of the brain that are activated during a learning task can become active again during sleep.

▼ Figure 49.9

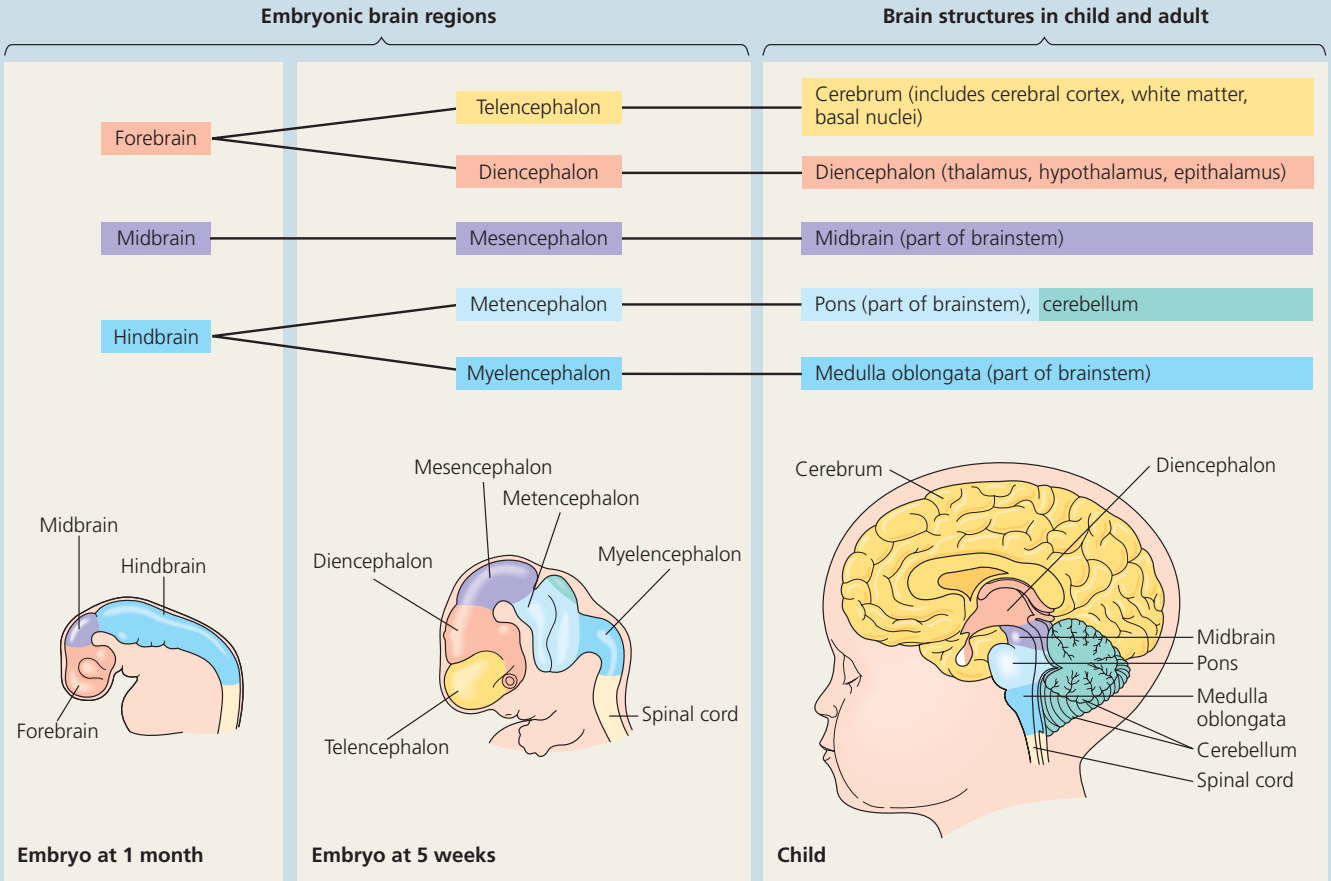
Exploring The Organization of the Human Brain

The brain is the most complex organ in the human body. Surrounded by the thick bones of the skull, the brain is divided into a set of distinctive structures, some of which are visible in the magnetic resonance image (MRI) of an adult's head shown at right. The diagram below traces the development of these structures in the embryo. Their major functions are explained on the facing page.



Human Brain Development

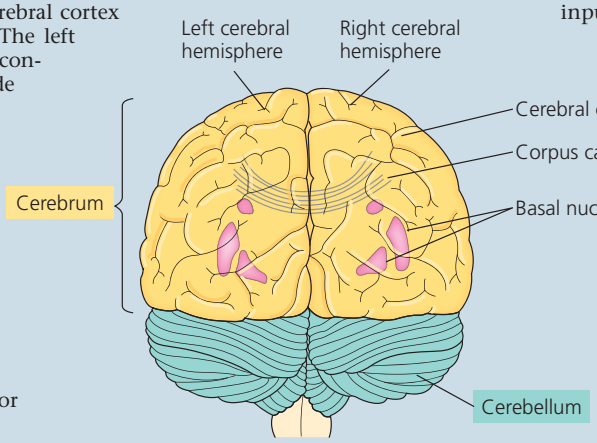
As a human embryo develops, the neural tube forms three anterior bulges—the **forebrain**, **midbrain**, and **hindbrain**—that together produce the adult brain. The midbrain and a part of the hindbrain give rise to the **brainstem**, a stalk that joins with the spinal cord at the base of the brain. The rest of the hindbrain gives rise to the **cerebellum**, which lies behind the brainstem. The third anterior bulge, the forebrain, develops into the diencephalon, including the neuroendocrine tissues of the brain, and the telencephalon, which becomes the **cerebrum**. Rapid, expansive growth of the telencephalon during the second and third months causes the outer portion, or cortex, of the cerebrum to extend over and around much of the rest of the brain.



The Cerebrum

The cerebrum controls skeletal muscle contraction and is the center for learning, emotion, memory, and perception. It is divided into right and left **cerebral hemispheres**. The **cerebral cortex** is vital for perception, voluntary movement, and learning.

Like the rest of the cerebrum, the cerebral cortex is divided into right and left sides. The left side receives information from, and controls the movement of, the right side of the body, and vice versa. A thick band of axons known as the **corpus callosum** enables the right and left cerebral cortices to communicate. Deep within the white matter, clusters of neurons called *basal nuclei* serve as centers for planning and learning movement sequences. Damage to these sites during fetal development can result in cerebral palsy, a disorder resulting from a disruption in the transmission of motor commands to the muscles.



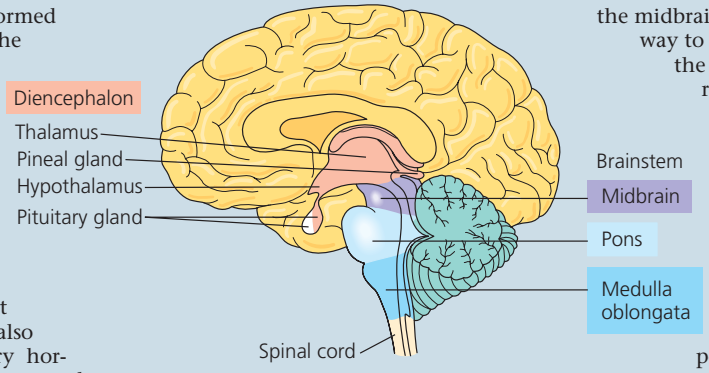
Adult brain viewed from the rear

The Cerebellum

The cerebellum coordinates movement and balance and helps in learning and remembering motor skills. The cerebellum receives sensory information about the positions of the joints and the lengths of the muscles, as well as input from the auditory (hearing) and visual systems. It also monitors motor commands issued by the cerebrum. The cerebellum integrates this information as it carries out coordination and error checking during motor and perceptual functions. Hand-eye coordination is an example of cerebellar control; if the cerebellum is damaged, the eyes can follow a moving object, but they will not stop at the same place as the object. Hand movement toward the object will also be erratic.

The Diencephalon

The diencephalon gives rise to the thalamus, hypothalamus, and epithalamus. The **thalamus** is the main input center for sensory information going to the cerebrum. Incoming information from all the senses is sorted in the thalamus and sent to the appropriate cerebral centers for further processing. The thalamus is formed by two masses, each roughly the size and shape of a walnut. A much smaller structure, the **hypothalamus**, contains the body's thermostat as well as the central biological clock. Through its control of the pituitary gland, the hypothalamus regulates hunger and thirst, plays a role in sexual and mating behaviors, and controls the fight-or-flight response. The hypothalamus is also the source of posterior pituitary hormones and of releasing hormones that act on the anterior pituitary (see Figures 45.15 and 45.17). The *epithalamus* includes the pineal gland, the source of melatonin. It also contains one of several clusters of capillaries that generate cerebrospinal fluid from blood.

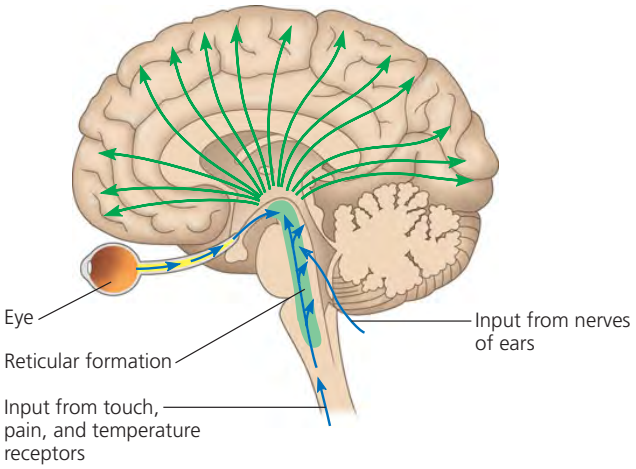


The Brainstem

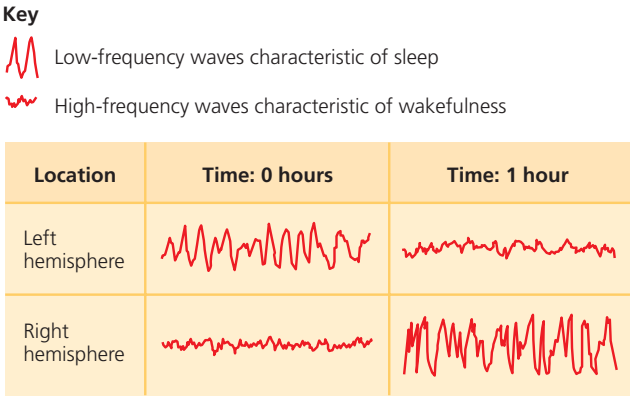
The brainstem consists of the midbrain, the **pons**, and the **medulla oblongata** (commonly called the *medulla*). The midbrain receives and integrates several types of sensory information and sends it to specific regions of the forebrain. All sensory axons involved in hearing either terminate in the midbrain or pass through it on their way to the cerebrum. In addition, the midbrain coordinates visual reflexes, such as the peripheral vision reflex: The head turns toward an object approaching from the side without the brain having formed an image of the object.

A major function of the pons and medulla is to transfer information between the PNS and the midbrain and forebrain. The pons and medulla also help coordinate large-scale body movements, such as running and climbing.

Most axons that carry instructions about these movements cross from one side of the CNS to the other in the medulla. As a result, the right side of the brain controls much of the movement of the left side of the body, and vice versa. An additional function of the medulla is the control of several automatic, homeostatic functions, including breathing, heart and blood vessel activity, swallowing, vomiting, and digestion. The pons also participates in some of these activities; for example, it regulates the breathing centers in the medulla.



▲ **Figure 49.10 The reticular formation.** This system of neurons distributed throughout the core of the brainstem filters sensory input (blue arrows), blocking familiar and repetitive information that constantly enters the nervous system. It sends the filtered input to the cerebral cortex (green arrows).



▲ **Figure 49.11 Dolphins can be asleep and awake at the same time.** EEG recordings were made separately for the two sides of a dolphin's brain. Low-frequency activity was recorded in one hemisphere while higher-frequency activity typical of being awake was recorded in the other hemisphere.

Arousal and sleep are controlled in part by the **reticular formation**, a diffuse network of neurons in the core of the brainstem **(Figure 49.10)**. Acting as a sensory filter, the reticular formation determines which incoming information reaches the cerebrum. The more information the cerebrum receives, the more alert and aware a person is, although the brain often ignores certain stimuli while actively processing other inputs. Besides the diffuse reticular formation, there are also specific parts of the brainstem that regulate sleep and wakefulness: The pons and medulla contain centers that cause sleep when stimulated, and the midbrain has a center that causes arousal.

All birds and mammals show characteristic sleep/wake cycles. Melatonin, a hormone produced by the pineal gland, appears to play an important role in these cycles. As you read in Chapter 45, peak melatonin secretion occurs at night.

Some animals display evolutionary adaptations that allow for substantial activity during sleep. Bottlenose dolphins, for example, swim while sleeping, rising to the surface to breathe air on a regular basis. How do they manage this feat? A critical clue came from American physiologist John Lilly, who in 1964 observed that dolphins sleep with one eye open and one closed. As in humans and other mammals, the forebrain of dolphins is physically and functionally divided into two halves, the right and left hemispheres. Lilly suggested that a dolphin sleeping with one eye closed could mean that just one side of the brain was asleep. In 1977, Russian scientist Lev Mukhametov set out to test Lilly's hypothesis by collecting EEG recordings from each hemisphere of sleeping dolphins **(Figure 49.11)**. Mukhametov's findings demonstrate that dolphins do in fact sleep with one brain hemisphere at a time.

Biological Clock Regulation

Cycles of sleep and wakefulness are just one example of a circadian rhythm, a daily cycle of biological activity. Such cycles occur in organisms ranging from bacteria to fungi, plants, insects, birds, and humans. As in other organisms, circadian rhythms in mammals rely on a **biological clock**, a molecular mechanism that directs periodic gene expression and cellular activity. Although biological clocks are typically synchronized to the cycles of light and dark in the environment, they can maintain a roughly 24-hour cycle even in the absence of environmental cues (see Figure 40.9). For example, humans kept in a constant environment exhibit a cycle length of 24.2 hours, with very little variation among individuals.

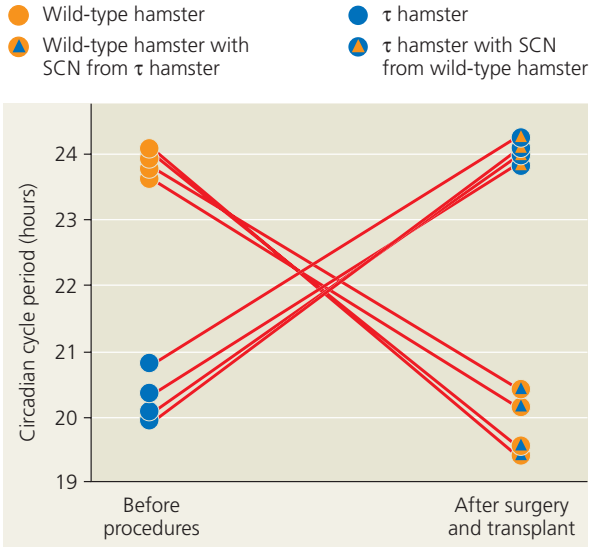
What normally links an animal's biological clock to environmental cycles of light and dark? In mammals, circadian rhythms are coordinated by a group of neurons in the hypothalamus called the **suprachiasmatic nucleus**, or **SCN**. (Certain clusters of neurons in the CNS are referred to as "nuclei.") In response to transmission of sensory information by the eyes, the SCN acts as a pacemaker, synchronizing the biological clock in cells throughout the body to the natural cycles of day length. By surgically removing the SCN from laboratory animals and then observing their behavior, scientists demonstrated that the SCN is required for circadian rhythms: Animals without an SCN lack rhythmicity in behaviors and in electrical activity of the brain. These experiments did not, however, reveal whether rhythms originate in the SCN or elsewhere. In 1990, researchers answered this question with the aid of a mutation that changes the circadian rhythm of hamsters **(Figure 49.12)**. By transplanting brain tissue between normal and mutant hamsters, these scientists demonstrated that the SCN determines the circadian rhythm of the whole animal.

▼ **Figure 49.12** **INQUIRY**

Which cells control the circadian rhythm in mammals?

EXPERIMENT The τ (tau) mutation alters the period of the circadian rhythm in Syrian (golden) hamsters (*Mesocricetus auratus*). Whereas wild-type hamsters have a circadian cycle lasting 24 hours in the absence of external cues, hamsters homozygous for the τ mutation have a cycle lasting only about 20 hours. To determine if the SCN controls the circadian rhythm, Michael Menaker and colleagues at the University of Virginia surgically removed the SCN from wild-type and τ hamsters. Several weeks later, each of these hamsters received a transplant of an SCN from a hamster of the opposite genotype. The researchers then measured the circadian cycle period of the transplant recipients.

RESULTS In 80% of the hamsters in which the SCN had been removed, transplanting an SCN from another hamster restored rhythmic activity. For hamsters in which an SCN transplant restored a circadian rhythm, the net effect of the two procedures (SCN destruction and replacement) on circadian rhythm is graphed below. Each of the eight lines represents the change in the observed circadian cycle period for an individual hamster.



CONCLUSION Because the circadian rhythm of the animal that received the transplant was that of the donor animal, regardless of whether the recipient was wild-type or τ mutant, cells associated with the suprachiasmatic nucleus must determine the period of the circadian rhythm.

SOURCE M. R. Ralph, R. G. Foster, F. C. Davis, and M. Menaker, Transplanted suprachiasmatic nucleus determines circadian period, *Science* 247:975–978 (1990).

WHAT IF? Suppose in the course of your research you identified a hamster mutant that lacked rhythmic activity. How might you use this mutant in transplant experiments with wild-type or τ mutant hamsters to demonstrate that the mutation affected the pacemaker function of the SCN?

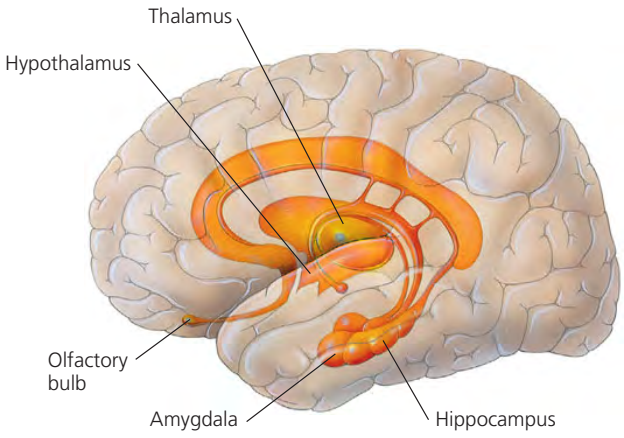
Emotions

Whereas a single structure in the brain controls the biological clock, the generation and experience of emotions depend on many brain structures, including the amygdala, hippocampus, and parts of the thalamus **(Figure 49.13)**. These structures border the brainstem in mammals and are therefore grouped as the *limbic system* (from the Latin *limbus*, border). The limbic system, however, is not dedicated solely to emotion. It also functions in motivation, olfaction (the sense of smell), behavior, and memory.

Generating emotion and experiencing emotion require parts of the brain in addition to the limbic system. For example, emotions that manifest themselves in behaviors such as laughing and crying involve an interaction of parts of the limbic system with sensory areas of the cerebrum. Structures in the forebrain also attach emotional "feelings" to basic, survival-related functions controlled by the brainstem, including aggression, feeding, and sexuality.

Emotional experiences are often stored as memories that can be recalled by similar circumstances. In the case of fear, emotional memory is stored separately from the memory system that supports explicit recall of events. The brain structure with the most important role in storage of emotional memory is the **amygdala**, an almond-shaped mass of nuclei (clusters of neurons) located near the base of the cerebrum.

To study the function of the human amygdala, researchers sometimes present adult subjects with an image followed by an unpleasant experience, such as a mild electrical shock. After several trials, study participants experience *autonomic arousal*—as measured by increased heart rate or sweating—if they see the image again. Subjects with brain damage confined to the amygdala can recall the image because their explicit memory is intact. However, they do not exhibit autonomic arousal, indicating that damage to the amygdala has resulted in a reduced capacity for emotional memory.



▲ **Figure 49.13** **The limbic system.**

Today, the amygdala and other brain structures are being studied with functional imaging methods that are transforming our understanding of the normal and diseased brain **(Figure 49.14)**.

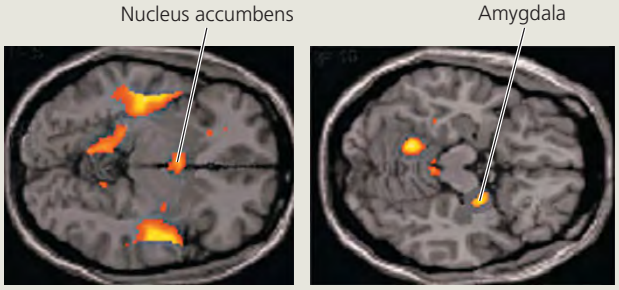
▼ Figure 49.14

IMPACT

Using Functional Brain Imaging to Map Activity in the Working Brain

Techniques for mapping brain activity have transformed the study of human brain function. The first widely used technique was positron-emission tomography (PET; see Figure 2.7). After injecting radioactive glucose into the blood of a subject, researchers can use PET scans to monitor metabolic activity across the brain. Further progress has come with functional magnetic resonance imaging (fMRI). In fMRI, the subject lies with his or her head in the center of a large, doughnut-shaped magnet. When the brain is scanned with electromagnetic waves, changes in blood oxygen concentration in active parts of the brain generate a signal that can be recorded.

Functional brain imaging has been applied to the study of human cognition, consciousness, and emotion. For example, functional imaging suggests that consciousness may be an emergent property of the brain based on activity in many areas of the cortex. In the experiment shown here, researchers explored differences in brain activity associated with music that listeners described as happy or sad. Listening to happy music activated the *nucleus accumbens*, a brain structure important for the perception of pleasure. In contrast, subjects who heard sad music had increased activity in the amygdala, a brain structure that serves as a center for emotional memory.



WHY IT MATTERS Functional brain imaging is aiding the investigation of recovery from stroke and other brain traumas, as well as helping map abnormalities in migraine headaches, dyslexia, and many psychiatric disorders. Functional imaging is also having a major impact on brain surgery. For example, for patients with epilepsy that is not responsive to drug therapy, functional imaging can pinpoint the region of abnormal function, increasing the effectiveness of surgery and enhancing recovery. Finally, functional imaging has been used to explore sex-based differences in the CNS, demonstrating, for instance, that cerebral blood flow is higher on average in women than in men.

FURTHER READING R. C. deCharms, Applications of real-time fMRI, *Nature Reviews Neuroscience* 9:720–729 (2008).

WHAT IF? In the experiment illustrated above, some regions of the brain showed activity under all conditions. What function might such regions carry out?

CONCEPT CHECK 49.2

1. When you wave your right hand, what part of your brain initiates the action?
2. When a police officer stops a driver for driving erratically and suspects that the person is intoxicated, the officer may ask the driver to close his or her eyes and touch his or her nose. What can you deduce from this test about one of the brain regions affected by alcohol?
3. **WHAT IF?** Suppose you examine individuals with damage to the CNS that has resulted in either coma (a prolonged state of unconsciousness) or general paralysis (a loss of skeletal muscle function throughout the body). Relative to the position of the reticular formation, where would you predict the site of injury to lie in each group of patients? Explain.

For suggested answers, see Appendix A.

CONCEPT 49.3

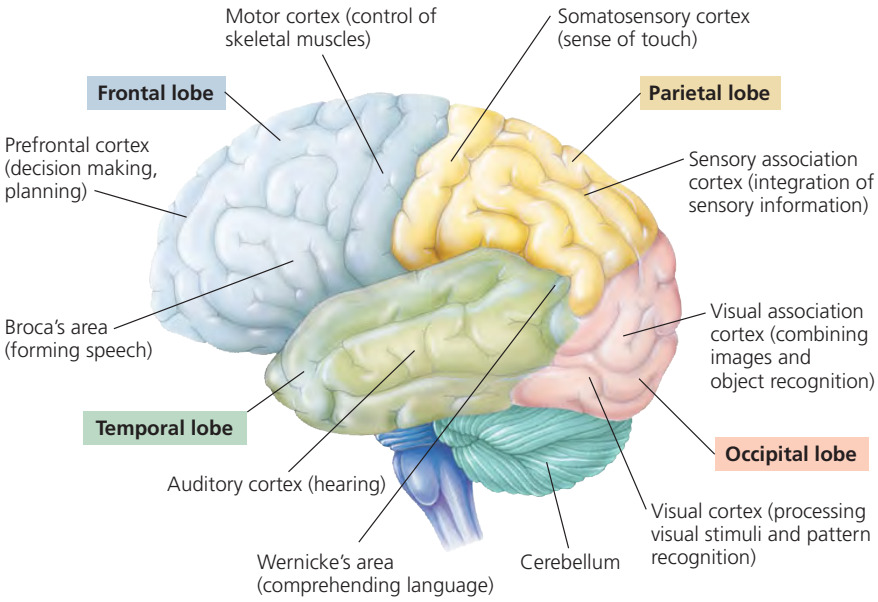
The cerebral cortex controls voluntary movement and cognitive functions

We turn now to the cerebrum, the part of the brain essential for awareness of our surroundings, language, cognition, memory, and consciousness. As shown in Figure 49.9, the cerebrum is the largest structure in the human brain. Like the brain overall, it exhibits regional specialization. For the most part, cognitive functions reside in the cortex, the outer layer of the cerebrum. Within the cortex, sensory areas receive and process sensory information, association areas integrate the information, and motor areas transmit instructions to other parts of the body.

In discussing the location of particular functions in the cerebral cortex, neurobiologists often use four regions, or *lobes*, as physical landmarks. As shown in **Figure 49.15**, each side of the cerebral cortex has a frontal, temporal, occipital, and parietal lobe (each is named for a nearby bone of the skull).

Language and Speech

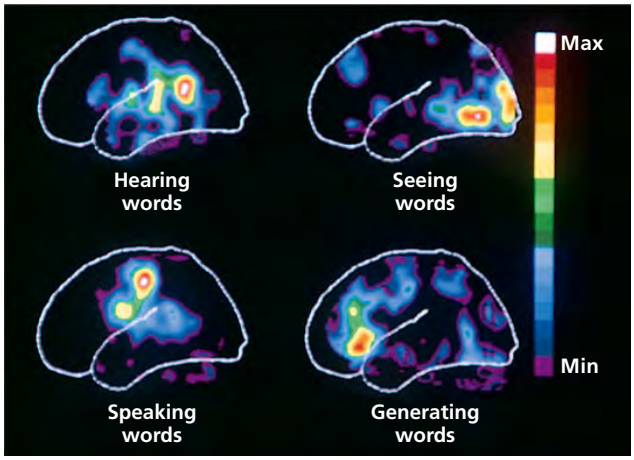
The mapping of higher cognitive functions to specific brain areas began in the 1800s when physicians learned that damage to particular regions of the cortex by injuries, strokes, or tumors can produce distinctive changes in a person's behavior. The French physician Pierre Broca conducted postmortem (after death) examinations of patients who had been able to understand language but unable to speak. He discovered that many of these patients had defects in a small region of the left frontal lobe, now known as *Broca's area*, that controls muscles in the face. The German physician Karl Wernicke found that damage to a posterior portion of the left temporal lobe, now



◀ Figure 49.15 The human cerebral cortex. Each side of the cerebral cortex is divided into four lobes, and each lobe has specialized functions, some of which are listed here. Some areas on the left side of the brain (shown here) have different functions from those on the right side (not shown).

called *Wernicke's area*, abolished the ability to comprehend speech but not the ability to speak.

More than a century after the discoveries of Broca and Wernicke, functional imaging studies confirmed that Broca's area is active during speech generation (**Figure 49.16**, lower left image) and Wernicke's area is active when speech is heard (Figure 49.16, upper left image). In addition, researchers have found that these areas belong to a much larger network of brain regions involved in language. Reading a printed word without speaking activates the visual cortex (Figure 49.16, upper right image), whereas reading a printed word out loud activates both the visual cortex and Broca's area. Frontal and temporal areas become active when meaning must be attached to words, such as when a person generates verbs to go with nouns or groups related words or concepts (Figure 49.16, lower right image).



▲ Figure 49.16 Mapping language areas in the cerebral cortex. These PET images show regions with different activity levels in one person's brain during four activities, all related to speech.

Lateralization of Cortical Function

Both Broca's area and Wernicke's area reside in the left cortical hemisphere, reflecting a significantly greater role with regard to language for the left side of the cerebrum than for the right side. The two hemispheres also make distinct contributions to some other brain functions, although to a lesser degree than for language. For example, the left hemisphere is more adept at math and logical operations. In contrast, the right hemisphere appears to be dominant in the recognition of faces and patterns, spatial relations, and nonverbal thinking. The establishment of these differences in hemisphere function in humans is called **lateralization**.

At least some lateralization relates to handedness, the preference for using one hand for certain motor activities. Across human populations, roughly 90% of individuals are more skilled with their right hand than with their left hand. Studies using fMRI have revealed how language processing differs in relation to handedness. When subjects thought of words without speaking out loud, brain activity was localized to the left hemisphere in 96% of right-handed subjects but in only 76% of left-handed subjects.

The two hemispheres normally work together harmoniously, trading information back and forth through the fibers of the corpus callosum. The importance of this exchange is revealed in patients whose corpus callosum has been surgically severed (a treatment of last resort for the most extreme forms of epilepsy, a seizure disorder). Individuals with a severed corpus callosum exhibit a "split-brain" effect. When a familiar word appears in their left field of vision, they cannot read the word: The sensory information that travels

from the left field of vision to the right hemisphere cannot reach the language centers in the left hemisphere. Each hemisphere in such patients functions independently of the other.

Information Processing

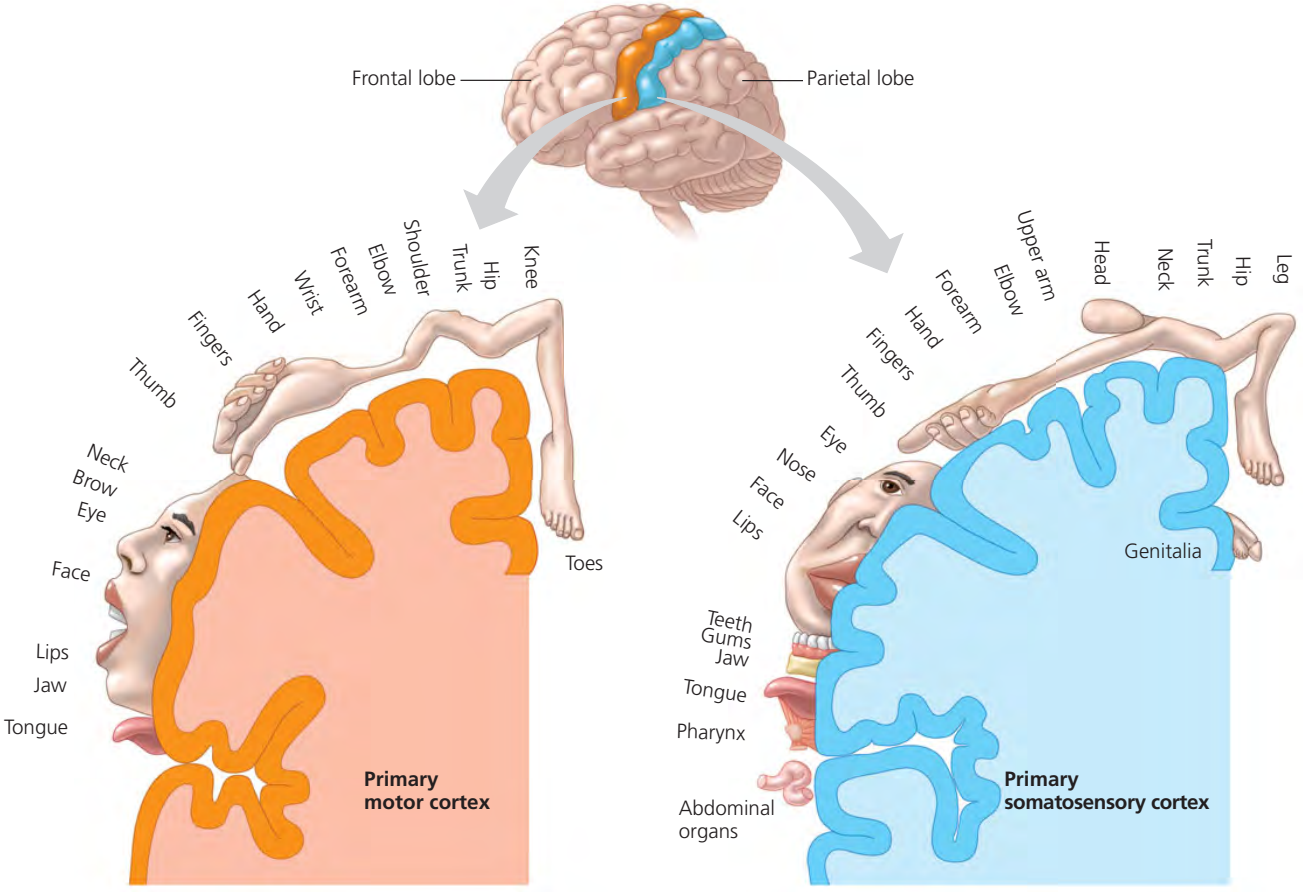
As you will learn further in Chapter 50, some of the sensory input to the cerebral cortex comes from groups of receptors clustered in dedicated sensory organs, such as the eyes and nose. Other sensory input originates in individual receptors in the hands, scalp, and elsewhere in the body. These somatic sensory, or *somatosensory*, receptors (from the Greek *soma*, body) provide information about touch, pain, pressure, temperature, and the position of muscles and limbs.

Most sensory information coming into the cortex is directed via the thalamus to primary sensory areas within the brain lobes. The thalamus directs different types of input to distinct locations. For example, visual information is sent to the occipital lobe, whereas auditory input is directed to the temporal lobe (see Figure 49.15).

Information received at the primary sensory areas is passed along to nearby association areas, which process particular features in the sensory input. In the occipital lobe, for instance, some groups of neurons in the primary visual area are specifically sensitive to rays of light oriented in a particular direction. In the visual association area, information related to such features is combined in a region dedicated to recognizing complex images, such as faces.

Integrated sensory information passes to the prefrontal cortex, which helps plan actions and movement. The cerebral cortex may then generate motor commands that cause particular behaviors—moving a limb or saying hello, for example. These commands consist of action potentials produced by neurons in the motor cortex, which lies at the rear of the frontal lobe (see Figure 49.15). The action potentials travel along axons to the brainstem and spinal cord, where they excite motor neurons, which in turn excite skeletal muscle cells.

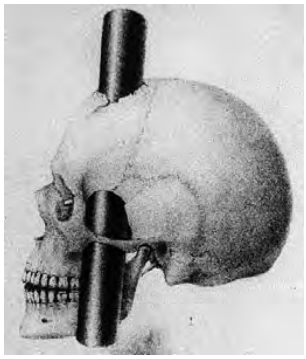
In the somatosensory cortex and motor cortex, neurons are arranged according to the part of the body that generates the sensory input or receives the motor commands **(Figure 49.17)**. For example, neurons that process sensory information from the legs and feet lie in the region of the somatosensory cortex closest to the midline. Neurons that control muscles in the



▲ **Figure 49.17 Body part representation in the primary motor and primary somatosensory cortices.** In these cross-sectional maps of the cortices, the cortical surface area devoted to each body part is represented by the relative size of that part in the cartoons.

legs and feet are located in the corresponding region of the motor cortex. Notice in Figure 49.17 that the cortical surface area devoted to each body part is not proportional to the size of the part. Instead, surface area correlates with the extent of neuronal control needed (for the motor cortex) or with the number of sensory neurons that extend axons to that part (for the somatosensory cortex). Thus, the surface area of the motor cortex devoted to the face is much larger than that devoted to the trunk, reflecting the extensive involvement of facial muscles in communication.

Frontal Lobe Function



In 1848, a horrific workplace accident pointed to the role of the prefrontal cortex in temperament and decision making. Phineas Gage was working as the foreman of a railroad construction crew when an explosion drove a meter-long iron rod through his head. The rod, which was more than 3 cm in diameter at one end, entered his skull just below his left eye and exited through the top of his head, damaging large portions of his frontal lobe. Astonishingly, Gage recovered. His personality, however, changed dramatically. He became emotionally detached, impatient, and erratic in his behavior.

Although the connection between Gage's brain injury and his personality change is a subject of debate, some tumors that develop in the frontal lobe cause symptoms that are similar to those of Gage. Intellect and memory seem intact, but decision making is flawed and emotional responses are diminished. In the 20th century, the same problems were observed as a result of frontal lobotomy, a surgical procedure that severs the connection between the prefrontal cortex and the limbic system. Together, these observations provide evidence that the frontal lobes have a substantial influence on what are often called "executive functions."

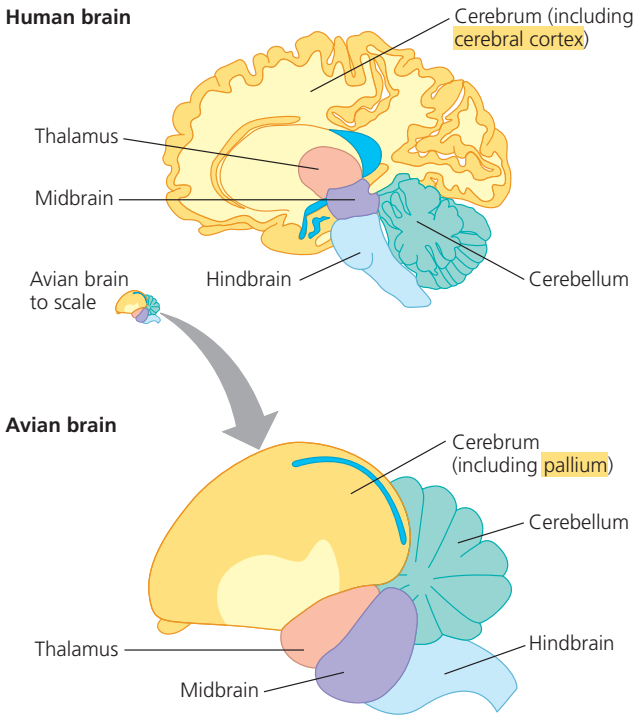
Frontal lobotomy was once a common treatment for severe behavioral disorders but later was abandoned as a medical practice. Behavioral disorders are now typically treated with medications, as discussed later in this chapter.

Evolution of Cognition in Vertebrates

EVOLUTION In humans, the cerebral cortex accounts for about 80% of total brain mass and is highly convoluted (see Figure 49.9). The convolutions allow the cerebral cortex to have a large surface area and still fit inside the skull: Less than 5 mm thick, it has a surface area of approximately 1,000 cm^2. The outermost part of the human cerebral cortex forms the *neocortex*, six parallel layers of neurons arranged tangential to the brain surface.

It was long thought that a highly convoluted neocortex was required for advanced *cognition*, the perception and reasoning that constitute knowledge. Primates and cetaceans (whales, dolphins, and porpoises) possess an extensively convoluted neocortex. However, birds lack such a structure and were thought to have much lower intellectual capacity. Experiments in recent years have refuted this idea. Western scrub jays (*Aphelocoma californica*) can remember the relative period of time that has passed after they stored and hid specific food items. New Caledonian crows (*Corvus moneduloides*) are highly skilled at making and using tools, an ability otherwise well documented only for humans and some other apes. African gray parrots (*Psittacus erithacus*) understand numerical and abstract concepts, distinguishing between "same" and "different" and grasping the idea of "none."

The anatomical basis for sophisticated information processing in birds appears to be the grouping of nuclei within the *pallium*, the top or outer portion of the brain **(Figure 49.18)**. This arrangement is different from that in the human pallium—the cerebral cortex—which contains flat sheets of cells in six layers. Thus, there are two types of pallium, each of which supports complex and flexible brain function.



▲ **Figure 49.18 Comparison of regions for higher cognition in avian and human brains.** Although structurally different, the cerebral cortex of the human brain (top cross section) and the pallium of a songbird brain (bottom cross section) have similar roles in higher cognitive activities and make many similar connections with other brain structures.

How did the differences between the bird pallium and human pallium arise during evolution? The current consensus is that the common ancestor of birds and mammals had a pallium in which neurons were organized into nuclei, as is still found in birds. Early in mammalian evolution, this nuclear (clustered) organization of neurons was transformed into a layered one. Connectivity was maintained during this transformation such that, for example, the thalamus relays sensory input relating to sights, sounds, and touch to the pallium in both birds and mammals.

Sophisticated information processing depends not only on the overall organization of a brain but also on the very small-scale changes that enable learning and encode memory. We'll turn to these changes in the context of humans in the next section.

CONCEPT CHECK 49.3

1. How can studying individuals with damage to a particular brain region provide insight into the normal function of that region?
2. Two brain areas important in the generation or perception of speech are Broca's area and Wernicke's area. How is the function of each area related to the activity of the surrounding portion of the cerebral cortex?
3. **WHAT IF?** If a woman with a severed corpus callosum viewed a photograph of a familiar face, first in her left field of vision and then in her right field, why would she find it difficult to put a name to the face in either field?

For suggested answers, see Appendix A.

CONCEPT 49.4

Changes in synaptic connections underlie memory and learning

During embryonic development, regulated gene expression and signal transduction establish the overall structure of the nervous system (see Chapter 47). Two processes then dominate the remaining development and remodeling of the nervous system. The first is a competition among neurons for survival. Neurons compete for growth-supporting factors, which are produced in limited quantities by tissues that direct neuron growth. Cells that don't reach the proper locations fail to receive such factors and undergo programmed cell death. The competition is so severe that half of the neurons formed in the embryo are eliminated. The net effect is the preferential survival of neurons that are located properly within the nervous system.

Synapse elimination is the second major process that shapes the nervous system. A developing neuron forms numerous synapses, more than are required for its proper function. The activity of that neuron then stabilizes some synapses and destabilizes others. By the end of embryonic development, neurons on average have lost more than half of their initial synapses, leaving behind the connections that survive into adulthood.

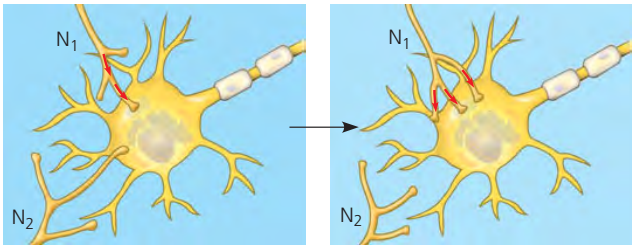
Together, neuron death and synapse elimination set up the basic network of cells and connections within the nervous system required throughout life.

Neural Plasticity

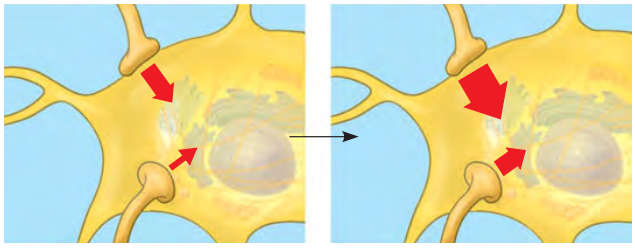
Although the overall organization of the CNS is established during embryonic development, it can change after birth. This capacity for the nervous system to be remodeled, especially in response to its own activity, is called **neural plasticity**.

Much of the reshaping of the nervous system occurs at synapses. When the activity of a synapse correlates with that of other synapses, changes may occur that reinforce that synaptic connection. Conversely, when the activity of a synapse fails to correlate with that of other synapses, the synaptic connection sometimes becomes weaker. In this way, synapses belonging to circuits that link information in useful ways are maintained, whereas those that convey bits of information lacking any context may be lost.

Figure 49.19a illustrates how these processes can result in either the addition or loss of a synapse. If you think of signals



(a) Connections between neurons are strengthened or weakened in response to activity. High-level activity at the synapse of the postsynaptic neuron with presynaptic neuron N_1 leads to recruitment of additional axon terminals from that neuron. Lack of activity at the synapse with presynaptic neuron N_2 leads to loss of functional connections with that neuron.



(b) If two synapses on the same postsynaptic cell are often active at the same time, the strength of the postsynaptic response may increase at both synapses.

▲ **Figure 49.19 Neural plasticity.** Synaptic connections can change over time, depending on the activity level at the synapse.

in the nervous system as traffic on a highway, such changes are comparable to adding or removing an entrance ramp. The net effect is to increase signaling between particular pairs of neurons and decrease signaling between other pairs. As shown in **Figure 49.19b**, changes can also strengthen or weaken signaling at a synapse. In our traffic analogy, this would be equivalent to widening or narrowing an entrance ramp.

Research indicates that *autism*, a developmental disorder that first appears early in childhood, involves a disruption of activity-dependent remodeling at synapses. Children affected with autism display impaired communication and social interaction, as well as stereotyped and repetitive behaviors.

Although the underlying causes of autism are unknown, there is a strong genetic contribution to this and related disorders. Extensive research has ruled out a link to vaccine preservatives, once proposed as a potential risk factor. Further understanding of the autism-associated disruption in synaptic plasticity may help efforts to better understand and treat this disorder.

Remodeling and refining of the nervous system occur in many contexts. For instance, soon after birth, the visual cortex of the mammalian brain undergoes reorganization in response to input from the optic nerve triggered by visual stimuli. Experiments have shown that this remodeling is a necessary step in the development of normal visual ability.

Remodeling of functional brain circuitry also occurs in diseases and injuries to the nervous system from which significant recovery is possible. One example is the treatment for a condition called phantom limb syndrome, in which a person feels pain or discomfort that seems to originate from an arm or leg that has been amputated. Having the patient view a reflection of the remaining limb in a mirrored box can reorganize the brain's neural connections in a way that eliminates the unpleasant feelings from the lost limb.

Memory and Learning

The formation of memories is another example of neural plasticity. Though we may not be aware of it, we are constantly checking what is happening against what just happened a few moments ago. We hold information for a time in **short-term memory** locations and then release it if it becomes irrelevant. If we wish to retain knowledge of a name, phone number, or other fact, the mechanisms of **long-term memory** are activated. If we later need to recall the name or number, we fetch it from long-term memory and return it to short-term memory.

Scientists have long wondered where in the brain short-term and long-term memories are located. We now know that both types of memory involve the storage of information in the cerebral cortex. In short-term memory, this information is accessed via temporary links formed in the hippocampus. When memories are made long-term, the links in the hippocampus are replaced by more permanent connections within the cerebral cortex itself. Some of this consolidation of memory is thought to occur during sleep. Furthermore, the reactivation of the hippocampus that is required for memory consolidation likely forms the basis for at least some of our dreams.

According to our current understanding of memory, the hippocampus is essential for acquiring new long-term memories but not for maintaining them. This hypothesis readily explains the symptoms of some individuals who suffer damage to the hippocampus: They cannot form any new lasting memories but can freely recall events from before their injury. In effect, their lack of normal hippocampal function traps them in their past.

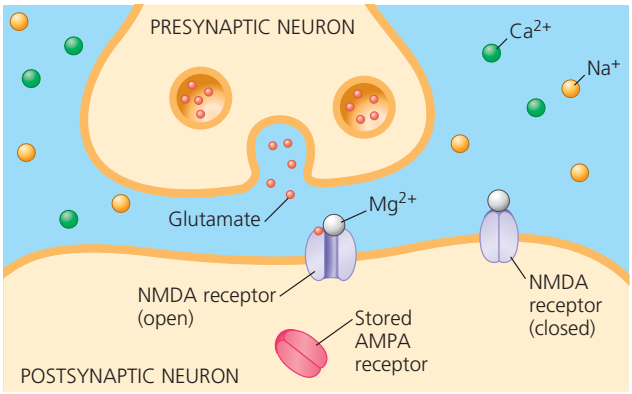
What evolutionary advantage might be offered by organizing short-term and long-term memories differently? Current thinking is that the delay in forming connections in the cerebral cortex allows long-term memories to be integrated gradually into the existing store of knowledge and experience, providing a basis for more meaningful associations. Consistent with this idea, the transfer of information from short-term to long-term memory is enhanced by the association of new data with data previously learned and stored in long-term memory. For example, it's easier to learn a new card game if you already have "card sense" from playing other card games.

Motor skills, such as walking, tying your shoes, or writing, are usually learned by repetition. You can perform these skills without consciously recalling the individual steps required to do these tasks correctly. Learning skills and procedures, such as those required to ride a bicycle, appears to involve cellular mechanisms very similar to those responsible for brain growth and development. In such cases, neurons actually make new connections. In contrast, memorizing phone numbers, facts, and places—which can be very rapid and may require only one exposure to the relevant item—may rely mainly on changes in the strength of existing neuronal connections. Next we will consider one way that such changes in strength can take place.

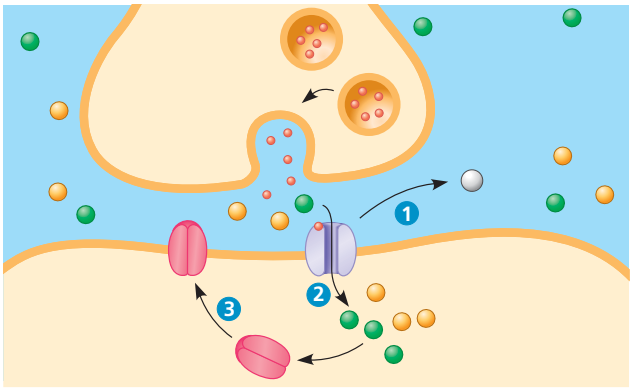
Long-Term Potentiation

In searching for the physiological basis of memory, researchers have concentrated their attention on processes that can alter a synaptic connection, making the flow of communication either more efficient or less efficient. We will focus here on **long-term potentiation (LTP)**, a lasting increase in the strength of synaptic transmission.

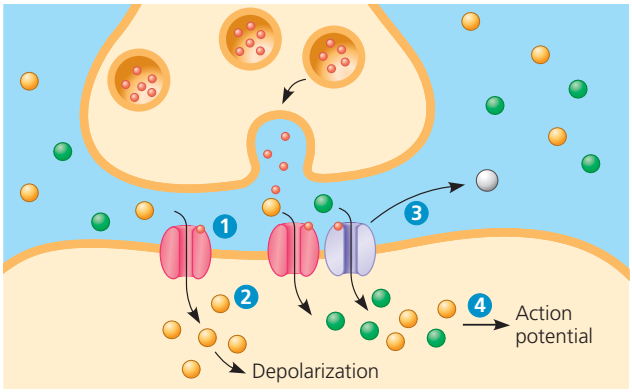
First characterized in tissue slices from the hippocampus, LTP involves a presynaptic neuron that releases the excitatory neurotransmitter glutamate. For LTP to occur, there must be a high-frequency series of action potentials in this presynaptic neuron. In addition, these action potentials must arrive at the synaptic terminal at the same time that the postsynaptic cell receives a depolarizing stimulus at another synapse.



(a) Synapse prior to long-term potentiation (LTP). The NMDA glutamate receptors open in response to glutamate but are blocked by Mg^{2+}.



(b) Establishing LTP. Activity at nearby synapses (not shown) depolarizes the postsynaptic membrane, causing 1 Mg^{2+} release from NMDA receptors. The unblocked receptors respond to glutamate by allowing 2 an influx of Na^+ and Ca^{2+}. The Ca^{2+} influx triggers 3 insertion of stored AMPA glutamate receptors into the postsynaptic membrane.



(c) Synapse exhibiting LTP. Glutamate release activates 1 AMPA receptors that trigger 2 depolarization. The depolarization unblocks 3 NMDA receptors. Together, the AMPA and NMDA receptors trigger postsynaptic potentials strong enough to initiate 4 action potentials without input from other synapses. Additional mechanisms (not shown) contribute to LTP, including receptor modification by protein kinases.

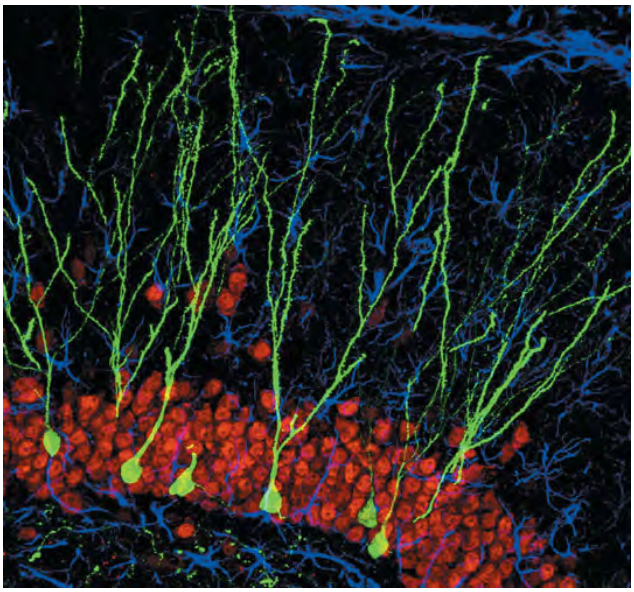
▲ **Figure 49.20 Long-term potentiation in the brain.**

LTP involves two types of glutamate receptors, each named for a molecule—NMDA or AMPA—that artificially activates that particular receptor. As shown in **Figure 49.20**, the set of receptors present on the postsynaptic membrane changes in response to an active synapse and a depolarizing stimulus. The result is LTP—a stable increase in the size of the postsynaptic potentials at the synapse. Because LTP can last for days or weeks in dissected tissue, it is thought to represent one of the fundamental processes by which memories are stored and learning takes place.

Stem Cells in the Brain

In 1998, Fred Gage, at the Salk Institute in California, and Peter Ericksson, at the Sahlgrenska University Hospital in Sweden, discovered that the adult human brain contains neural stem cells. Recall from Chapters 20 and 46 that stem cells retain the ability to divide indefinitely. While some of their progeny remain undifferentiated, others differentiate into specialized cells. Studies with mice reveal that stem cells in the brain give rise to neurons that mature, migrate to particular locations in the hippocampus, and become incorporated into the circuitry of the adult nervous system **(Figure 49.21)**. Evidence from other studies indicates that such neurons play an essential role in learning and memory. In this manner, adult neural stem cells contribute to the plasticity that enables remodeling of brain circuitry in response to experience.

Researchers are now tackling the challenge of finding a way to use neural stem cells as a means of replacing brain tissue



▲ **Figure 49.21 Newly born neurons in the hippocampus of an adult mouse.** In this light micrograph, new neurons derived from adult stem cells are labeled with green fluorescent protein (GFP), and all neurons are labeled with a red dye that binds DNA.

that has ceased to function properly. Unlike the PNS, the mammalian CNS cannot fully repair itself when damaged or diseased. Surviving neurons in the brain can make new connections and sometimes compensate for damage, as occurs in the remarkable recoveries of some stroke victims. Generally, however, brain and spinal cord injuries, strokes, and disorders that destroy CNS neurons, such as Alzheimer's disease and Parkinson's disease, have devastating and irreversible effects.

Although stem cell therapy for the brain is likely to be a long way off, the recent discovery that expression of just four particular genes converts differentiated adult cells to stem cells (see Chapter 20) represents significant progress in this endeavor.

CONCEPT CHECK 49.4

1. Outline two mechanisms by which the flow of information between two neurons in adults can increase.
2. Individuals with localized brain damage have been very useful in the study of many brain functions. Why is this unlikely to be true for consciousness?
3. **WHAT IF?** Suppose that a person with damage to the hippocampus is unable to acquire new long-term memories. Why might the acquisition of short-term memories also be impaired?

For suggested answers, see Appendix A.

CONCEPT 49.5

Many nervous system disorders can be explained in molecular terms

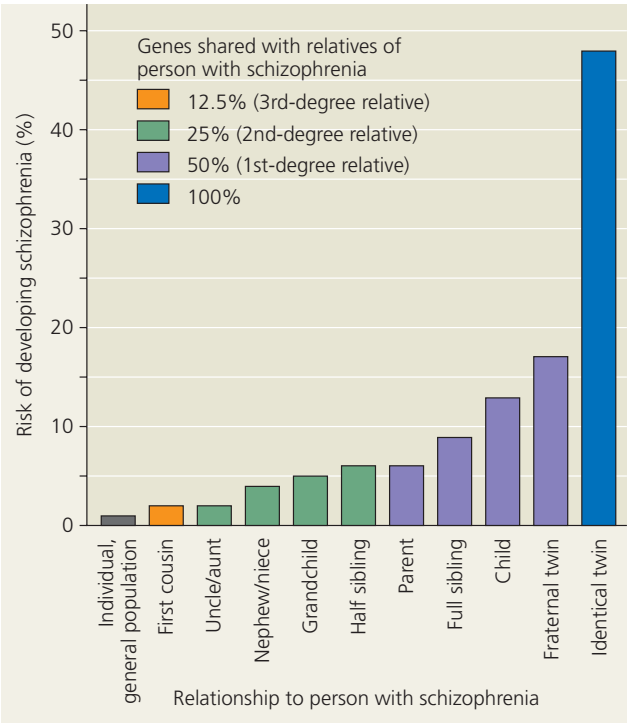
Disorders of the nervous system, including schizophrenia, depression, drug addiction, Alzheimer's disease, and Parkinson's disease, are a major public health problem. Together, they result in more hospitalizations in the United States than do heart disease or cancer. Until recently, hospitalization was typically the only available treatment, and many affected individuals were institutionalized for the rest of their lives. Today, many disorders that alter mood or behavior can be treated with medication, reducing average hospital stays for these disorders to only a few weeks. At the same time, societal attitudes are changing as awareness grows that nervous system disorders often result from chemical or anatomical changes in the brain. Many challenges remain, however, especially for Alzheimer's and other diseases that lead to nervous system degeneration.

Major research efforts are under way to identify genes that cause or contribute to disorders of the nervous system. Identifying such genes offers hope for identifying causes, predicting outcomes, and developing effective treatments. For most nervous system disorders, however, genetic contributions only partially account for which individuals are affected. The other significant contribution to disease comes from environmental factors. Unfortunately, environmental contributions are typically very difficult to identify.

To distinguish between genetic and environmental variables, scientists often carry out family studies. In such studies, researchers track how family members are related genetically, which individuals are affected, and which family members grew up in the same household. These studies are especially informative when one of the affected individuals has either an identical twin or an adopted sibling who is genetically unrelated. The results of family studies indicate that certain nervous system disorders, such as schizophrenia, have a very strong genetic component **(Figure 49.22)**.

Schizophrenia

About 1% of the world's population suffer from **schizophrenia**, a severe mental disturbance characterized by psychotic episodes in which patients have a distorted perception of reality. People with schizophrenia typically experience hallucinations (such as "voices" that only they can hear) and delusions (for example, the idea that others are plotting to harm them). Despite the commonly held notion,



▲ **Figure 49.22 Genetic contribution to schizophrenia.** First cousins, uncles, and aunts of a person with schizophrenia have twice the risk of unrelated members of the population of developing the disease. The risks for closer relatives are many times greater.

schizophrenia does not necessarily result in multiple personalities. Rather, the name *schizophrenia* (from the Greek *schizo*, split, and *phren*, mind) refers to the fragmentation of what are normally integrated brain functions.

Two lines of evidence suggest that schizophrenia affects neuronal pathways that use dopamine as a neurotransmitter. First, the drug amphetamine ("speed"), which stimulates dopamine release, can produce the same set of symptoms as schizophrenia. Second, many of the drugs that alleviate the symptoms of schizophrenia block dopamine receptors. Schizophrenia may also alter glutamate signaling, since the street drug "angel dust," or PCP, blocks glutamate receptors and induces strong schizophrenia-like symptoms.

Fortunately, medications frequently can alleviate the major symptoms of schizophrenia. Although the first treatments developed often had substantial negative side effects, newer medications are equally effective and much safer to use. Ongoing research aimed at identifying the genetic mutations that contribute to schizophrenia may yield new insights about the causes of the disease and lead to even more effective therapies.

Depression

Depression is a disorder characterized by depressed mood, as well as abnormalities in sleep, appetite, and energy level. Two broad forms of depressive illness are known: major depressive disorder and bipolar disorder. Individuals affected by **major depressive disorder** undergo periods—often lasting many months—during which once enjoyable activities provide no pleasure and provoke no interest. One of the most common nervous system disorders, major depression affects about one in every seven adults at some point, and twice as many women as men.

Bipolar disorder, or manic-depressive disorder, involves swings of mood from high to low and affects about 1% of the world's population. The manic phase is characterized by high self-esteem, increased energy, a flow of ideas, overtalkativeness, and increased risk taking. In its milder forms, this phase is sometimes associated with great creativity, and some well-known artists, musicians, and literary figures (including Vincent Van Gogh, Robert Schumann, Virginia Woolf, and Ernest Hemingway, to name a few) have had very productive periods during manic phases. The depressive phase comes with lowered ability to feel pleasure, loss of motivation, sleep disturbances, and feelings of worthlessness. These symptoms can be so severe that affected individuals attempt suicide.

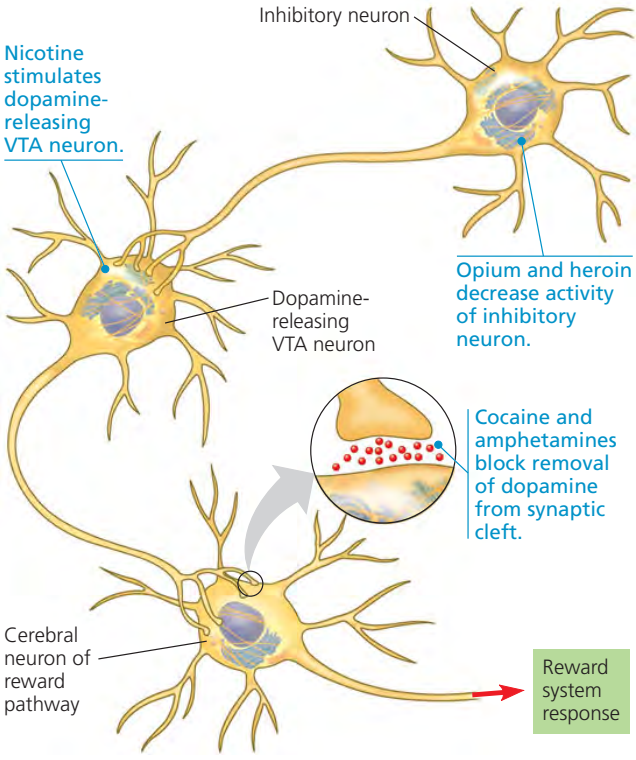
Major depressive and bipolar disorders are among the nervous system disorders for which available therapies are most effective. Many drugs used to treat depressive illness, including fluoxetine (Prozac), increase the activity of biogenic amines in the brain.

Drug Addiction and the Brain's Reward System

Drug addiction is a disorder characterized by compulsive consumption of a drug and loss of control in limiting intake. Addictive drugs include stimulants, such as cocaine and amphetamine, and sedatives, such as heroin. However, all of these drugs, as well as alcohol and nicotine, are addictive for the same reason: Each increases activity of the brain's reward system, neural circuitry that normally functions in pleasure, motivation, and learning.

In the absence of drug addiction, the reward system of the brain provides motivation for activities that enhance survival and reproduction, such as eating in response to hunger, drinking when thirsty, and engaging in sexual activity when aroused. In addicted individuals, "wanting" is instead directed toward further drug consumption.

As shown in **Figure 49.23**, inputs to the reward system are received by neurons in a region near the base of the brain called the *ventral tegmental area (VTA)*. When activated, these neurons release dopamine from their synaptic terminals in



▲ **Figure 49.23 Effects of addictive drugs on the reward system of the mammalian brain.** Addictive drugs alter the transmission of signals in the pathway formed by neurons of the ventral tegmental area (VTA).

MAKE CONNECTIONS *Based on what you learned in Concept 48.3 (pp. 1050–1051), what effect would you expect if you depolarized the neurons in the VTA? Explain.*

specific regions of the cerebrum, including the *nucleus accumbens* (see Figure 49.14).

Addictive drugs affect the reward system in several ways. First, each drug has an immediate and direct effect that enhances the activity of the dopamine pathway (see Figure 49.23). As addiction develops, there are also long-lasting changes in the reward circuitry. The result is a craving for the drug independent of any pleasure associated with consumption.

Laboratory animals have proved especially useful in teaching us how the brain's reward system works and how particular drugs affect its function. Rats, for example, will provide themselves with cocaine, heroin, or amphetamine when given a dispensing system linked to a lever in their cage. Furthermore, they exhibit addictive behavior in such circumstances, continuing to self-administer the drug rather than seek food, even to the point of starvation.

As scientists expand their knowledge about the brain's reward system and the various forms of addiction, there is hope that the insights will lead to more effective prevention and treatment.

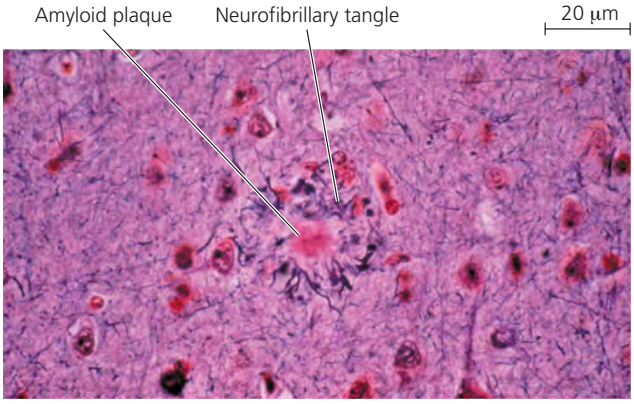
Alzheimer's Disease

Alzheimer's disease is a mental deterioration, or dementia, characterized by confusion and memory loss. Its incidence is age related, rising from about 10% at age 65 to about 35% at age 85. The disease is progressive, with patients gradually becoming less able to function and eventually needing to be dressed, bathed, and fed by others. Moreover, patients with Alzheimer's disease often lose their ability to recognize people, including their immediate family, and may treat them with suspicion and hostility.

Alzheimer's disease leads to the death of neurons in many areas of the brain, including the hippocampus and cerebral cortex. As a result, there is often massive shrinkage of brain tissue. Postmortem examination of the remaining brain tissue reveals two characteristic features—amyloid plaques and neurofibrillary tangles **(Figure 49.24)**.

The plaques are aggregates of β-amyloid, an insoluble peptide that is cleaved from the extracellular portion of a membrane protein found in neurons. Membrane enzymes, called secretases, catalyze the cleavage, causing β-amyloid to accumulate in plaques outside the neurons. It is these plaques that appear to trigger the death of surrounding neurons.

The neurofibrillary tangles observed in Alzheimer's disease are primarily made up of the tau protein. (This protein is unrelated to the tau mutation that affects circadian rhythm in hamsters.) The tau protein normally helps assemble and maintain microtubules that transport nutrients along axons. In Alzheimer's disease, tau undergoes changes that cause it to bind to itself, resulting in neurofibrillary tangles. There is evidence that changes in tau are associated with the appearance of early-onset Alzheimer's disease, a much less common disorder that affects relatively young individuals.



▲ **Figure 49.24 Microscopic signs of Alzheimer's disease.** A hallmark of Alzheimer's disease is the presence in brain tissue of neurofibrillary tangles surrounding plaques made of β-amyloid (LM).

There is currently no cure for Alzheimer's disease, but an enormous effort has led to the recent development of drugs that are partially effective in relieving some of the symptoms. Doctors are also beginning to use functional brain imaging to diagnose Alzheimer's disease in patients exhibiting early signs of dementia.

Parkinson's Disease

Symptoms of **Parkinson's disease**, a motor disorder, include muscle tremors, poor balance, a flexed posture, and a shuffling gait. Facial muscles become rigid, limiting the ability of patients to vary their expressions. Like Alzheimer's disease, Parkinson's disease is a progressive brain illness and is more common with advancing age. The incidence of Parkinson's disease is about 1% at age 65 and about 5% at age 85. In the U.S. population, approximately 1 million people are afflicted.

The symptoms of Parkinson's disease result from the death of neurons in the midbrain that normally release dopamine at synapses in the basal nuclei. As with Alzheimer's disease, protein aggregates accumulate. Most cases of Parkinson's disease lack an identifiable cause; however, a rare form of the disease that appears in relatively young adults has a clear genetic basis. Molecular studies of mutations linked to this early-onset Parkinson's disease reveal disruption of genes required for certain mitochondrial functions. Researchers are investigating whether mitochondrial defects also contribute to the more common and later-onset form of the disease.

At present there is no cure for Parkinson's disease. Approaches used to manage the symptoms include brain

surgery, deep-brain stimulation, and drugs such as L-dopa, a molecule that can cross the blood-brain barrier and be converted to dopamine in the CNS. One potential cure is to implant dopamine-secreting neurons, either in the midbrain or in the basal nuclei. Laboratory studies of this strategy show promise: In rats with an experimentally induced condition that mimics Parkinson's disease, implanting dopamine-secreting neurons can lead to a recovery of motor control. Whether this regenerative approach can also work in humans is one of many important questions in modern brain research.

CONCEPT CHECK 49.5

1. Compare Alzheimer's disease and Parkinson's disease.
2. How is dopamine activity related to schizophrenia, drug addiction, and Parkinson's disease?
3. **WHAT IF?** If you could detect early-stage Alzheimer's disease, would you expect to see brain changes that were similar to, although less extensive than, those seen in patients who have died of this disease? Explain.

For suggested answers, see Appendix A.

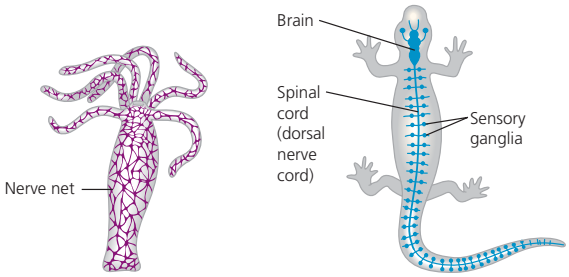
49 CHAPTER REVIEW

SUMMARY OF KEY CONCEPTS

CONCEPT 49.1

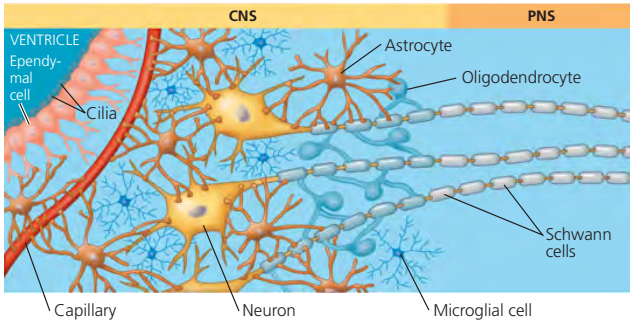
Nervous systems consist of circuits of neurons and supporting cells (pp. 1062–1067)

- Invertebrate nervous systems range in complexity from simple **nerve nets** to highly centralized nervous systems having complicated brains and ventral nerve cords.



Hydra (cnidarian) Salamander (vertebrate)

In vertebrates, the central nervous system (CNS), consisting of the brain and the spinal cord, integrates information, while the **nerves** of the peripheral nervous system (PNS) transmit sensory and motor signals between the CNS and the rest of the body. The simplest circuits in the vertebrate nervous system control **reflex** responses, in which sensory input is linked to motor output without involvement of the brain. Vertebrate neurons are supported by several types of glia, including **astrocytes**, oligodendrocytes, Schwann cells, and ependymal cells.

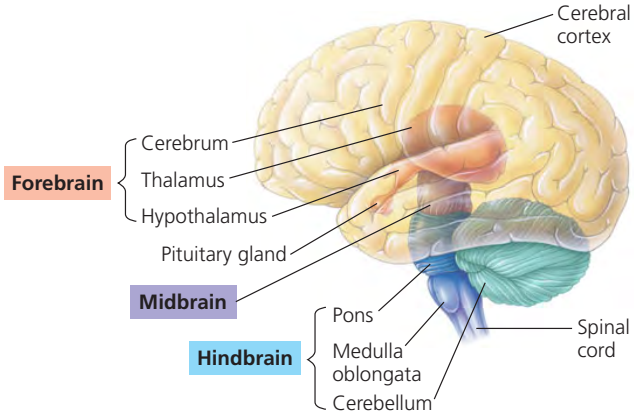


- Afferent neurons carry sensory signals to the CNS. Efferent neurons function in either the **motor system**, which carries signals to skeletal muscles, or the **autonomic nervous system**, which regulates smooth and cardiac muscles. The **sympathetic** and **parasympathetic divisions** of the autonomic nervous system have antagonistic effects on a diverse set of target organs, while the **enteric division** controls the activity of many digestive organs.

? *How does the circuitry of a reflex facilitate a rapid response?*

CONCEPT 49.2

The vertebrate brain is regionally specialized (pp. 1067–1072)



- The cerebrum has two hemispheres, each of which consists of cortical **gray matter** overlying **white matter** and basal nuclei, which are important in planning and learning movements. A thick band of axons, the **corpus callosum**, provides communication between the right and left cerebral cortices.
- Within each region of the brain, particular structures have specialized functions. The **pons** and **medulla oblongata** are relay stations for information traveling between the PNS and the cerebrum. The **reticular formation**, a network of neurons within the **brainstem**, regulates sleep and arousal. The **cerebellum** helps coordinate motor, perceptual, and cognitive functions. It is also involved in learning and remembering

motor skills. The **thalamus** is the main center through which sensory and motor information passes to the **cerebrum**. The **hypothalamus** regulates homeostasis and basic survival behaviors. Within the hypothalamus, the **suprachiasmatic nucleus (SCN)** acts as the pacemaker for circadian rhythms.

- The generation and experience of emotions involve many regions of the brain. However, the **amygdala** plays a key role in recognizing and recalling a number of emotions.

? *What role do particular regions of the brain play in vision and responses to visual input?*

CONCEPT 49.3

The cerebral cortex controls voluntary movement and cognitive functions (pp. 1072–1076)

- Each side of the **cerebral cortex** has four lobes—frontal, temporal, occipital, and parietal—that contain primary sensory areas and association areas. Specific types of sensory input enter the primary sensory areas. Association areas integrate information from different sensory areas.
- Portions of the frontal and temporal lobes, including Broca's area and Wernicke's area, are essential for generating and understanding language. These functions are concentrated in the left **cerebral hemisphere**, as are math and logic operations. The right hemisphere appears to be stronger at pattern recognition and nonverbal thinking. At least some of this **lateralization** of functions relates to handedness.
- In the somatosensory cortex and the motor cortex, neurons are distributed according to the part of the body that generates sensory input or receives motor commands.
- Primates and cetaceans, which are capable of higher cognition, have an extensively convoluted neocortex, the outermost part of the cerebral cortex. In birds, a brain region called the pallium contains clustered nuclei that carry out functions similar to those performed by the cerebral cortex of mammals. Some birds can solve problems and understand abstractions in a manner indicative of higher cognition.

? *After an accident, a patient has trouble with language and has paralysis on one side of the body. Which side would you expect to be paralyzed? Why?*

CONCEPT 49.4

Changes in synaptic connections underlie memory and learning (pp. 1076–1079)

- During development, more neurons and synapses form than will exist in the adult. The programmed death of neurons and elimination of synapses in embryos establish the basic structure of the nervous system. In the adult, reshaping of the nervous system can involve the loss or addition of synapses or the strengthening or weakening of signaling at synapses. This capacity for remodeling is termed **neural plasticity**. Defective remodeling of synapses is partly responsible for the developmental abnormalities of autism.
- **Short-term memory** relies on temporary links in the hippocampus. In **long-term memory**, these temporary links are replaced by connections within the cerebral cortex. This transfer of information from short-term to long-term memory is enhanced by the association of new data with that already in long-term memory. **Long-term potentiation (LTP)** is a lasting increase in the strength of synaptic transmission and appears to be an important process in memory storage and learning.
- The adult human brain contains stem cells that can differentiate into mature neurons. Therapy based on stem cells offers a potential method for replacing neurons lost to injury or disease.

? *Learning multiple languages is typically easier earlier in childhood than later in life. How does this fit with our understanding of neural development?*

CONCEPT 49.5

Many nervous system disorders can be explained in molecular terms (pp. 1079–1082)

- Research has identified the biochemical basis of a number of nervous system disorders. **Schizophrenia**, which is characterized by hallucinations, delusions, and other symptoms, affects neuronal pathways that use dopamine as a neurotransmitter. Drugs that increase the activity of biogenic amines in the brain can be used to treat **bipolar disorder** and **major depressive disorder**. The compulsive drug use that characterizes addiction reflects altered activity of the brain's reward system, which normally provides motivation for actions that enhance survival or reproduction.
- **Alzheimer's disease** and **Parkinson's disease** are neurodegenerative and typically age related. Alzheimer's disease is a dementia in which neurofibrillary tangles and amyloid plaques form in the brain. Parkinson's disease is a motor disorder caused by the death of dopamine-secreting neurons and associated with the presence of protein aggregates.

? *The fact that both amphetamines and PCP have effects similar to the symptoms of schizophrenia suggests a potentially complex basis for this disease. Explain.*

TEST YOUR UNDERSTANDING

LEVEL 1: KNOWLEDGE/COMPREHENSION

1. Wakefulness is regulated by the reticular formation, which is present in the
   a. basal nuclei.
   b. cerebral cortex.
   c. brainstem.
   d. limbic system.
   e. spinal cord.
2. Which of the following structures or regions is *incorrectly* paired with its function?
   a. limbic system—motor control of speech
   b. medulla oblongata—homeostatic control
   c. cerebellum—coordination of movement and balance
   d. corpus callosum—communication between the left and right cerebral cortices
   e. amygdala—emotional memory
3. Patients with damage to Wernicke's area have difficulty
   a. coordinating limb movement.
   b. generating speech.
   c. recognizing faces.
   d. understanding language.
   e. experiencing emotion.
4. The cerebral cortex plays a major role in all of the following *except*
   a. short-term memory.
   b. long-term memory.
   c. circadian rhythm.
   d. foot-tapping rhythm.
   e. breath holding.

LEVEL 2: APPLICATION/ANALYSIS

5. After suffering a stroke, a patient can see objects anywhere in front of him but pays attention only to objects in his right field of vision. When asked to describe these objects, he has difficulty judging their size and distance. What part of the brain was likely damaged by the stroke?
   a. the left frontal lobe
   b. the right frontal lobe
   c. the left parietal lobe
   d. the right parietal lobe
   e. the corpus callosum

6. Injury localized to the hypothalamus would most likely disrupt
   a. short-term memory.
   b. coordination during locomotion.
   c. executive functions, such as decision making.
   d. sorting of sensory information.
   e. regulation of body temperature.

7. **DRAW IT** The reflex that pulls your hand away when you prick your finger on a sharp object relies on a simple neuronal circuit with two synapses in the spinal cord. (a) Using a circle to represent a cross section of the spinal cord, draw the circuit, labeling the types of neurons, the direction of information flow in each, and the locations of synapses. (b) Draw a simple diagram of the brain indicating where pain would eventually be perceived.

LEVEL 3: SYNTHESIS/EVALUATION

8. **EVOLUTION CONNECTION**
   Scientists often use measures of "higher-order thinking" to assess intelligence in other animals. For example, birds are judged to have sophisticated thought processes because they can use tools and make use of abstract concepts. What problems do you see in defining intelligence in these ways?

9. **SCIENTIFIC INQUIRY**
   Consider an individual who had been fluent in American Sign Language before suffering damage to the left cerebral hemisphere. After the injury, this person could still understand signs, but could not readily generate signs that represented his thoughts. What two hypotheses could explain this finding, and how might you distinguish between them?

10. **SCIENCE, TECHNOLOGY, AND SOCIETY**
    With increasingly sophisticated methods for scanning brain activity, scientists are rapidly developing the ability to detect an individual's particular emotions and thought processes from outside the body. What benefits and problems do you envision when such technology becomes readily available?

11. **WRITE ABOUT A THEME**
    The Genetic Basis of Life In a short essay (100–150 words), explain how specification of the adult nervous system by the genome is incomplete.

For selected answers, see Appendix A.

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