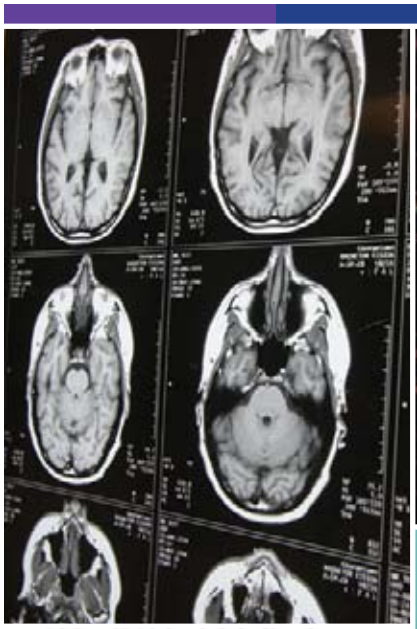
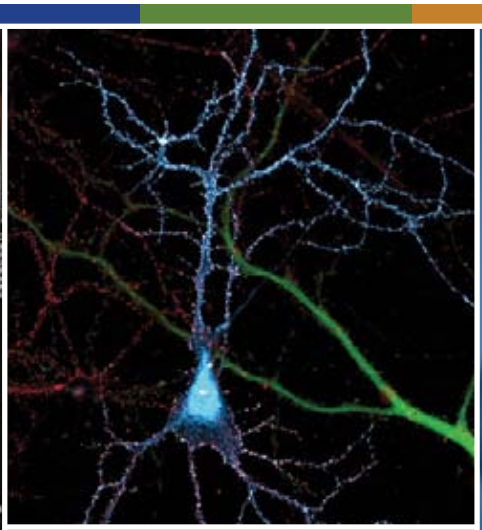
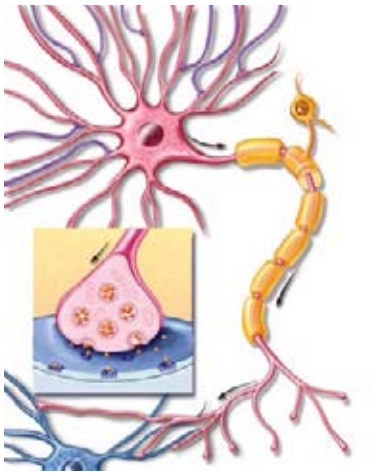
A Companion Publication to *BrainFacts.org*

BrainFacts

A PRIMER ON THE BRAIN AND NERVOUS SYSTEM







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A companion to BrainFacts.org

A PUBLIC INFORMATION INITIATIVE OF:

Preface

Over the past two decades, scientific knowledge about the structure and function of the brain and nervous system and understanding of brain-based disorders have increased exponentially. Neuroscientists are using remarkable new tools and technologies to learn how the brain controls and responds to the body, drives behavior, and forms the foundation for the mind. Research is also essential for the development of therapies for more than 1,000 nervous system disorders that affect more than 1 billion people worldwide.

As these strides occur, it is crucial that scientists communicate with the general public, helping students, teacher, parents, medical caregivers, policymakers, and others stay informed of developments in neuroscience. In particular, students — the scientists, policymakers and scientifically literate citizens of the future — need access to clear, easy-to-use information on this important topic.

As part of its enduring commitment to public education and outreach, the Society for Neuroscience (SfN) is pleased to present the seventh edition of *Brain Facts: A Primer on the Brain and Nervous System*. This edition has been substantially revised. Research progress has been updated throughout the publication, and a new section on animal research added. The information also has been reorganized into six sections to make it easier for readers to glean the "big ideas" covered, and the specific topics that fall under each category.

The publication of the *Brain Facts* seventh edition coincides with the launch of *BrainFacts.org*, a public information initiative of The Kavli Foundation, The Gatsby Charitable Foundation, and SfN. *BrainFacts.org* brings to digital life the historic *Brain Facts* book, and augments it with hundreds of additional, scientifically vetted public information resources available from leading neuroscience organizations worldwide. *BrainFacts.org* is envisioned as a dynamic and unique online source for authoritative public information about the progress and promise of brain research. It will be updated frequently with the latest neuroscience information from around the globe, while the *Brain Facts* book will continue to be a vital teaching and outreach tool.

We encourage you to visit *BrainFacts.org* frequently to supplement information found within this companion book, and to join us in the quest for continuing revolutionary advances in understanding the brain and mind.

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Introduction

THE HUMAN BRAIN — a spongy, three-pound mass of tissue — is the most complex living structure in the universe. With the capacity to create a network of connections that far surpasses any social network and stores more information than a supercomputer, the brain has enabled humans to achieve breathtaking milestones — walking on the moon, mapping the human genome, and composing masterpieces of literature, art, and music. What's more, scientists still have not uncovered the extent of what the brain can do. This single organ controls every aspect of our body, ranging from heart rate and sexual activity to emotion, learning, and memory. The brain controls the immune system's response to disease, and determines, in part, how well people respond to medical treatments. Ultimately, it shapes our thoughts, hopes, dreams, and imaginations. It is the ability of the brain to perform all of these functions that makes us human.

Neuroscientists, whose specialty is the study of the brain and the nervous system, have the daunting task of deciphering the mystery of how the brain commands the body. Over the years, the field has made enormous progress. For example, neuroscientists now know that each person has as many as 100 billion nerve cells called *neurons*, and the communication between these cells forms the basis of all brain function. However, scientists continue to strive for a deeper understanding of how these cells are born, grow, and organize themselves into effective, functional circuits that usually remain in working order for life.

The motivation of researchers is to further our understanding of human behavior, including how we read and speak and why we form relationships; to discover ways to prevent or cure many devastating disorders of the brain as well as the body under the brain's control; and to advance the enduring scientific quest to understand how the world around us — and within us — works.

The importance of this research cannot be overstated. More than 1,000 disorders of the brain and nervous system result in more hospitalizations than any other disease group, including heart disease and cancer. Neurological illnesses affect more than 50 million Americans annually and cost more than $500 billion to treat. In addition, mental disorders strike 44 million adults a year at a cost of $148 billion. Advances in research could reduce these costs. For example, discovering how to delay the onset of *Alzheimer's disease* by five years could save $50 billion in annual health care costs.

In the past two decades, neuroscience has made impressive progress in many of the field's key areas. Now, more than ever, neuroscience is on the cusp of major breakthroughs.

Recently, significant findings have been documented in the following areas.

Genetics

Disease genes have been identified that are key to several disorders, including the epilepsies, Alzheimer's disease, *Huntington's disease*, *Parkinson's disease*, and *amyotrophic lateral sclerosis* (ALS). These discoveries have provided new insight into underlying disease mechanisms and are beginning to suggest new treatments. With the mapping of the human genome, neuroscientists have been able to make more rapid progress in identifying genes that either contribute to or directly cause human neurological disease. Mapping animal genomes has aided the search for genes that regulate and control many complex behaviors.

Gene-Environment Interactions

Most major diseases have a genetic basis strongly influenced by the environment. For example, identical twins, who share the same DNA, have an increased risk of getting the same disease compared with nonidentical siblings. However, if one twin gets the disease, the probability the other will also be affected is between 30 percent and 60 percent, indicating that there are environmental factors at play as well. Environmental influences involve factors such as exposure to toxic substances, diet, level of physical activity, and stressful life events.

Brain Plasticity

The brain possesses the ability to modify neural connections to better cope with new circumstances. Scientists have begun to uncover the molecular basis of this process, called *plasticity*, revealing how learning and memory occur and how declines might be reversed. In addition, scientists have discovered that the adult brain continually generates new nerve cells — a

process known as *neurogenesis*. Interestingly, one of the most active regions for neurogenesis in the brain, the *hippocampus*, is also an area heavily involved in learning and memory.

New Therapies Researchers have gained insight into the mechanisms of molecular neuropharmacology, or how drugs affect the functioning of neurons in the nervous system, providing a new understanding of the mechanisms of addiction. These advances have also led to new treatments for depression and obsessive-compulsive disorder. In addition, neuroscientists have discovered that many of the toxic venoms used by animals can be adapted into new pharmacological treatments. For example, the poison of a puffer fish, tetrodotoxin (TTX), halts electrical signaling in nerve cells. However, in discrete, targeted doses, TTX can be used specifically to shut down those nerve cells involved in sending constant signals of chronic pain.

Imaging Revolutionary imaging techniques, including *positron emission tomography* (PET), *functional magnetic resonance imaging* (fMRI), and optical imaging with weak lasers, have revealed the brain systems underlying attention, memory, and emotions. These techniques also have pointed to dynamic changes that occur in *schizophrenia* and other disorders.

Cell Death Two major advances in neuroscience — the discovery of how and why neurons die, along with the discovery of *stem cells*, which divide and form new neurons — have many clinical applications. These findings have dramatically improved the chances of reversing the effects of injury in both the brain and the *spinal cord*. The first effective treatments for *stroke* and spinal cord injury based on these advances are under study.

Brain Development New understanding of brain function, as well as newly discovered molecules responsible for guiding nervous system development, have given scientists greater insight into certain disorders of childhood, such as cerebral palsy. Together with the discovery of stem cells, these advances are pointing to novel strategies for helping the brain or spinal cord regain functions lost as a result of injury or developmental dysfunction.

This book provides a glimpse of what is known about the nervous system, the disorders of the brain, and some of the exciting avenues of research that promise new therapies for many neurological diseases. In the years ahead, neuroscience research funded by public and private support will continue to expand our knowledge of how this extraordinary organ and the entire nervous system function.

Chapter 1: Brain Basics

In this Chapter

- Anatomy of the Brain and the Nervous System
- The Neuron
- Neurotransmitters and Neuromodulators

Anatomy of the Brain and the Nervous System

The brain is the body's control center, managing just about everything we do. Whether we're thinking, dreaming, playing sports, or even sleeping, the brain is involved in some way. A wonder of evolutionary engineering, the brain is organized into different parts that are wired together in a specific way. Each part has a specific job (or jobs) to do, making the brain the ultimate multitasker. Working in tandem with the rest of the nervous system, the brain sends and receives messages, allowing for ongoing communication.

Mapping the Brain

The *cerebrum*, the largest part of the human brain, is associated with higher order functioning, including the control of voluntary behavior. Thinking, perceiving, planning, and understanding language all lie within the cerebrum's control. The cerebrum is divided into two hemispheres — the right hemisphere and the left hemisphere. Bridging the two hemispheres is a bundle of fibers called the *corpus callosum*. The two hemispheres communicate with one another across the corpus callosum.

Covering the outermost layer of the cerebrum is a sheet of tissue called the *cerebral cortex*. Because of its gray color, the cerebral cortex is often referred to as *gray matter*. The wrinkled appearance of the human brain also can be attributed to characteristics of the cerebral cortex. More than two-thirds of this layer is folded into grooves. The grooves increase the brain's surface area, allowing for inclusion of many more neurons.

The function of the cerebral cortex can be understood by dividing it somewhat arbitrarily into zones, much like the geographical arrangement of continents.

The *frontal lobe* is responsible for initiating and coordinating motor movements; higher cognitive skills, such as problem solving, thinking, planning, and organizing; and for many aspects of personality and emotional makeup.

The *parietal lobe* is involved with sensory processes, attention, and language. Damage to the right side of the parietal lobe can result in difficulty navigating spaces, even familiar ones. If the left side is injured, the ability to understand spoken and/or written language may be impaired.

The *occipital lobe* helps process visual information, including recognition of shapes and colors.

The *temporal lobe* helps process auditory information and integrate information from the other senses. Neuroscientists also believe that the temporal lobe has a role to play in *short-term memory* through its hippocampal formation, and in learned emotional responses through its *amygdala*.

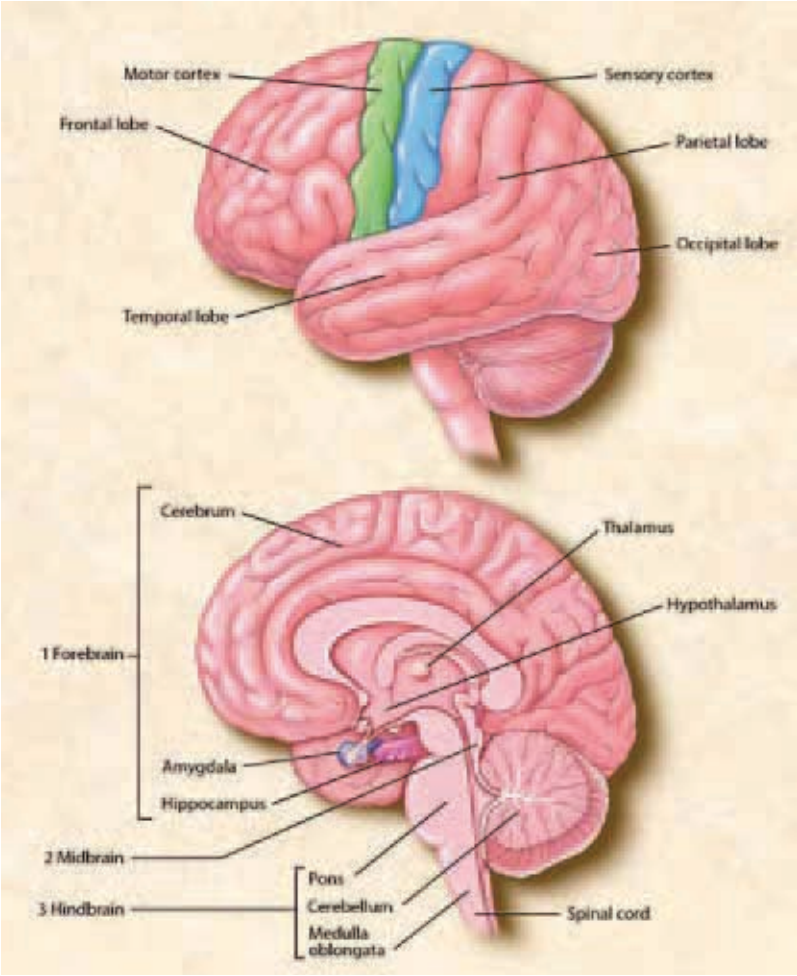
All of these structures make up the forebrain. Other key parts of the *forebrain* include the *basal ganglia*, which are cerebral nuclei deep in the cerebral cortex; the *thalamus*; and the *hypothalamus*. The cerebral nuclei help coordinate muscle movements and reward useful behaviors; the thalamus passes most sensory information on to the cerebral cortex after helping to prioritize it; and the hypothalamus is the control center for appetites, defensive and reproductive behaviors, and sleep-wakefulness.

The *midbrain* consists of two pairs of small hills called colliculi. These collections of neurons play a critical role in visual and auditory reflexes and in relaying this type of information to the thalamus. The midbrain also has clusters of neurons that regulate activity in widespread parts of the central nervous system and are thought to be important for reward mechanisms and mood.

The *hindbrain* includes the *pons* and the medulla oblongata, which control respiration, heart rhythms, and blood glucose levels.

Another part of the hindbrain is the *cerebellum* which, like the cerebrum, also has two hemispheres. The cerebellum's two hemispheres help control movement and cognitive processes that require precise timing, and also play an important role in Pavlovian learning.

The spinal cord is the extension of the brain through the *vertebral column*. It receives sensory information from all parts



The top image shows the four main sections of the cerebral cortex: the frontal lobe, the parietal lobe, the occipital lobe, and the temporal lobe. Functions such as movement are controlled by the motor cortex, and the sensory cortex receives information on vision, hearing, speech, and other senses. The bottom image shows the location of the brain's major internal structures.

of the body below the head. It uses this information for reflex responses to pain, for example, and it also relays the sensory information to the brain and its cerebral cortex. In addition, the spinal cord generates nerve impulses in nerves that control the muscles and the viscera, both through reflex activities and through voluntary commands from the cerebrum.

The Parts of the Nervous System

The forebrain, midbrain, hindbrain, and spinal cord form the central nervous system (CNS), which is one of two great divisions of the nervous system as a whole. The brain is protected by the skull, while the spinal cord, which is about 17 inches (43 cm) long, is protected by the vertebral column.

The other great division of the human brain is the *peripheral nervous system* (PNS), which consists of nerves and small concentrations of gray matter called ganglia, a term specifically used to describe structures in the PNS. Overall the nervous system is a vast biological computing device formed by a network of gray matter regions interconnected by *white matter* tracts.

The brain sends messages via the spinal cord to peripheral nerves throughout the body that serve to control the muscles and internal organs. The somatic nervous system is made up of neurons connecting the CNS with the parts of the body that interact with the outside world. Somatic nerves in the cervical region are related to the neck and arms; those in the thoracic region serve the chest; and those in the lumbar and sacral regions interact with the legs.

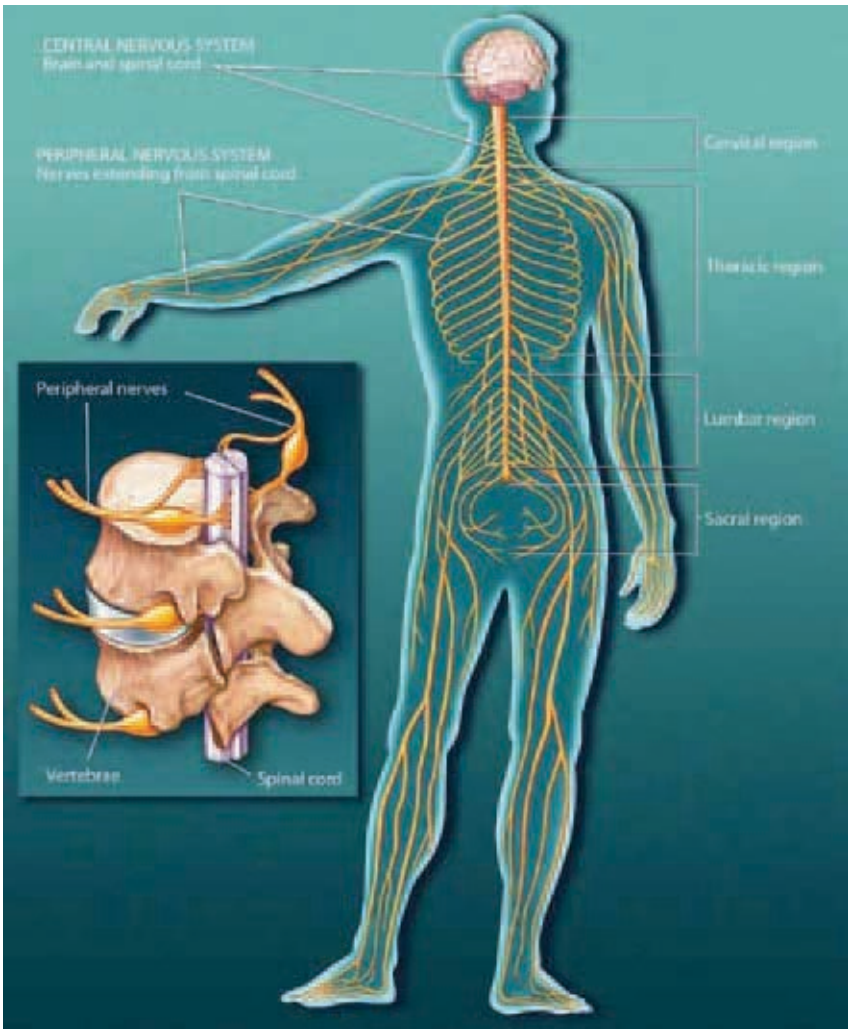
The *autonomic nervous system* is made of neurons connecting the CNS with internal organs. It is divided into two parts. The *sympathetic nervous system* mobilizes energy and resources during times of *stress* and arousal, while the *parasympathetic nervous system* conserves energy and resources during relaxed states, including sleep.

Messages are carried throughout the nervous system by the individual units of its circuitry: neurons. The next section describes the structure of neurons, how they send and receive messages, and recent discoveries about these unique cells.

The Neuron

Cells within the nervous system, called neurons, communicate with each other in unique ways. The neuron is the basic working unit of the brain, a specialized cell designed to transmit information to other nerve cells, muscle, or gland cells. In fact, the brain is what it is because of the structural and functional properties of interconnected neurons. The mammalian brain contains between 100 million and 100 billion neurons, depending on the species. Each mammalian neuron consists of a *cell body*, *dendrites*, and an *axon*. The cell body contains the nucleus and cytoplasm. The axon extends from the cell body and often gives rise to many smaller branches before ending at *nerve terminals*. Dendrites extend from the neuron cell body and receive messages from other neurons. *Synapses* are the contact points where one neuron communicates with another. The dendrites are covered with synapses formed by the ends of axons from other neurons.

When neurons receive or send messages, they transmit electrical impulses along their axons, which can range



The nervous system has two great divisions: the central nervous system (CNS), which consists of the brain and the spinal cord, and the peripheral nervous system (PNS), which consists of nerves and small concentrations of gray matter called ganglia. The brain sends messages via the spinal cord to the body's peripheral nerves, which control the muscles and internal organs.

in length from a tiny fraction of an inch (or centimeter) to three feet (about one meter) or more. Many axons are covered with a layered *myelin sheath*, which accelerates the transmission of electrical signals along the axon. This sheath is made by specialized cells called *glia*. In the brain, the glia that make the sheath are called oligodendrocytes, and in the peripheral nervous system, they are known as Schwann cells.

The brain contains at least ten times more glia than neurons. Glia perform many jobs. Researchers have known for a while that glia transport nutrients to neurons, clean up brain debris, digest parts of dead neurons, and help hold neurons in place. Current research is uncovering important new roles for glia in brain function.

Nerve impulses involve the opening and closing of *ion channels*. These are selectively permeable, water-filled molecular tunnels that pass through the cell membrane and allow *ions* — electrically charged atoms — or small molecules to enter or leave the cell. The flow of ions creates an electrical current that produces tiny voltage changes across the neuron's cell membrane.

The ability of a neuron to generate an electrical impulse depends on a difference in charge between the inside and outside of the cell. When a nerve impulse begins, a dramatic reversal in the electrical potential occurs on the cell's membrane, as the neuron switches from an internal negative charge to a positive charge state. The change, called an *action potential*, then passes along the axon's membrane at speeds up to several hundred miles per hour. In this way, a neuron may be able to fire impulses multiple times every second.

When these voltage changes reach the end of an axon, they trigger the release of *neurotransmitters*, the brain's chemical messengers. Neurotransmitters are released at nerve terminals, diffuse across the synapse, and bind to receptors on the surface of the target cell (often another neuron, but also possibly a muscle or gland cell). These receptors act as on-and-off switches for the next cell. Each receptor has a distinctly shaped region that selectively recognizes a particular chemical messenger. A neurotransmitter fits into this region in much the same way that a key fits into a lock. When the transmitter is in place, this interaction alters the target cell's membrane potential and triggers a response from the target cell, such as the generation of an action potential, the contraction of a muscle, the stimulation of enzyme activity, or the *inhibition* of neurotransmitter release.

An increased understanding of neurotransmitters in the brain and knowledge of the effects of drugs on these chemicals — gained largely through animal research — comprise one of the largest research efforts in neuroscience. Scientists hope that this information will help them become more knowledgeable about the circuits responsible for disorders such as Alzheimer's and Parkinson's diseases.

Sorting out the various chemical circuits is vital to understanding the broad spectrum of the brain's functions, including how the brain stores memories, why sex is such a powerful motivation, and what makes up the biological basis of mental illness.

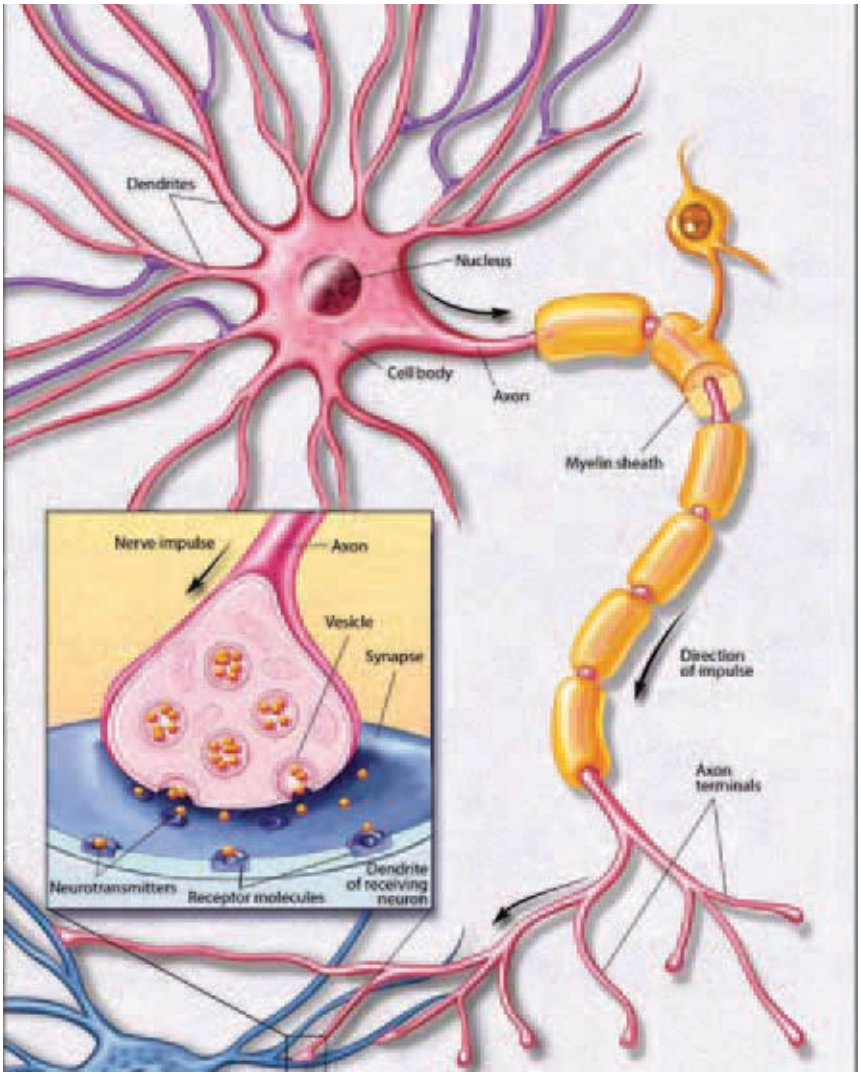
There are many different kinds of neurotransmitters, and they all play an essential role in the human body. The next section provides a summary of key neurotransmitters and neuromodulators, chemicals that help shape overall activity in the brain.

Neurotransmitters and Neuromodulators

Acetylcholine

The first neurotransmitter to be identified — about 80 years ago — was *acetylcholine* (ACh). This chemical is released by neurons connected to voluntary muscles, causing them to contract, and by neurons that control the heartbeat. ACh is also a transmitter in many regions of the brain.

ACh is synthesized in axon terminals. When an action potential arrives at the nerve terminal, electrically charged calcium ions rush in, and ACh is released into the synapse, where it attaches to ACh receptors on the target cells. On voluntary muscles, this action opens sodium channels and causes muscles to contract. ACh is then broken down by the enzyme acetylcholinesterase and resynthesized in the nerve terminal. Antibodies that block one type of ACh receptor cause *myasthenia gravis*, a disease characterized by fatigue and muscle weakness.



Neurons are cells within the nervous system that transmit information to other nerve cells, muscle, or gland cells. Most neurons have a cell body, an axon, and dendrites. The cell body contains the nucleus and cytoplasm. The axon extends from the cell body and often gives rise to many smaller branches before ending at nerve terminals. Dendrites extend from the neuron cell body and receive messages from other neurons. Synapses are the contact points where one neuron communicates with another. The dendrites are covered with synapses formed by the ends of axons from other neurons.

Much less is known about ACh in the brain. Recent discoveries suggest that it may be critical for normal attention, memory, and sleep. Because ACh-releasing neurons die in Alzheimer's patients, finding ways to restore this neurotransmitter is a goal of current research. Drugs that inhibit acetylcholinesterase — and increase ACh in the brain — are presently the main drugs used to treat Alzheimer's disease.

Amino Acids

Amino acids, widely distributed throughout the body and the brain, serve as the building blocks of proteins. Certain amino acids can also serve as neurotransmitters in the brain. The neurotransmitters glycine and *gamma-aminobutyric acid (GABA)* inhibit the firing of neurons. The activity of GABA is increased by benzodiazepines (e.g., valium) and by anticonvulsant drugs. In Huntington's disease, a hereditary disorder that begins during midlife, the GABA-producing neurons in brain centers that coordinate movement degenerate, causing uncontrollable movements. *Glutamate* and aspartate act as excitatory signals, activating, among others, N-methyl-d-

aspartate (NMDA) receptors which, in developing animals, have been implicated in activities ranging from learning and memory to development and specification of nerve contacts. The stimulation of *NMDA receptors* may promote beneficial changes in the brain, whereas overstimulation can cause nerve cell damage or cell death. This is what happens as a result of trauma and during a stroke. Developing drugs that block or stimulate activity at NMDA receptors holds promise for improving brain function and treating neurological and psychiatric disorders.

Catecholamines The term *catecholamines* includes the neurotransmitters *dopamine* and *norepinephrine*. Dopamine and norepinephrine are widely present in the brain and peripheral nervous system. Dopamine is present in three principal circuits in the brain. The dopamine circuit that regulates movement has been directly linked to disease. Due to dopamine deficits in the brain, people with Parkinson's disease show such symptoms as muscle tremors, rigidity, and difficulty in moving. Administration of levodopa, a substance from which dopamine is synthesized, is an effective treatment for Parkinson's, allowing patients to walk and perform skilled movements more successfully.

Another dopamine circuit is thought to be important for *cognition* and emotion; abnormalities in this system have been implicated in schizophrenia. Because drugs that block certain dopamine receptors in the brain are helpful in diminishing *psychotic* symptoms, learning more about dopamine is important to understanding mental illness. In a third circuit, dopamine regulates the endocrine system. Dopamine directs the hypothalamus to manufacture *hormones* and hold them in the *pituitary gland* for release into the bloodstream or to trigger the release of hormones held within cells in the pituitary.

Deficiencies in norepinephrine occur in patients with Alzheimer's disease, Parkinson's disease, and Korsakoff's syndrome, a cognitive disorder associated with chronic alcoholism. These conditions all lead to memory loss and a decline in cognitive functioning. Thus, researchers believe that norepinephrine may play a role in both learning and memory. Norepinephrine is also secreted by the sympathetic nervous system throughout the body to regulate heart rate and blood pressure. Acute stress increases release of norepinephrine from sympathetic nerves and the *adrenal medulla*, the innermost part of the adrenal gland.

Serotonin This neurotransmitter is present in the brain and other tissues, particularly blood platelets and the lining of the digestive tract. In the brain, *serotonin* has been identified as an important factor in sleep quality, mood, depression, and anxiety. Because serotonin controls different switches affecting various emotional states, scientists believe these switches can be manipulated by analogs, chemicals with molecular structures similar to that of serotonin. Drugs that alter serotonin's action, such as fluoxetine, relieve symptoms of depression and obsessive-compulsive disorder.

Peptides Short chains of amino acids that are linked together, *peptides* are synthesized in the cell body and greatly outnumber the classical transmitters discussed earlier. In 1973, scientists discovered receptors for opiates on neurons in several regions of the brain, suggesting that the brain must make substances very similar to opium. Shortly thereafter, scientists made their first discovery of an opiate peptide produced by the brain. This chemical resembles morphine, an opium derivative used medically to kill pain. Scientists named this substance enkephalin, literally meaning "in the head." Soon after, other types of opioid peptides were discovered. These were named *endorphins*, meaning "endogenous morphine." The precise role of the naturally occurring opioid peptides is unclear. A simple hypothesis is that they are released by brain neurons in times of stress to minimize pain and enhance adaptive behavior. Some sensory nerves — tiny unmyelinated C fibers — contain a peptide called substance P, which causes the sensation of burning pain. The active component of chili peppers, capsaicin, causes the release of substance P, something people should be aware of before eating them.

Trophic Factors Researchers have discovered several small proteins in the brain that act as *trophic factors*, substances that are necessary for the development, function, and survival of specific groups of neurons. These small proteins are made in brain cells, released locally in the brain, and bind to receptors expressed by specific neurons. Researchers also have identified genes that code for receptors and are involved in the signaling mechanisms of trophic factors. These findings are expected to result in a greater understanding of how trophic factors work in the brain. This information should also prove useful for the design of new therapies for brain disorders of development and for degenerative diseases, including Alzheimer's disease and Parkinson's disease.

Hormones In addition to the nervous system, the endocrine system is a major communication system of the body. While the nervous system uses neurotransmitters as

its chemical signals, the endocrine system uses hormones. The pancreas, kidneys, heart, adrenal glands, *gonads*, thyroid, parathyroid, thymus, and even fat are all sources of hormones. The endocrine system works in large part by acting on neurons in the brain, which controls the pituitary gland. The pituitary gland secretes factors into the blood that act on the *endocrine glands* to either increase or decrease hormone production. This is referred to as a feedback loop, and it involves communication from the brain to the pituitary to an endocrine gland and back to the brain. This system is very important for the activation and control of basic behavioral activities, such as sex; emotion; responses to stress; and eating, drinking, and the regulation of body functions, including growth, reproduction, energy use, and *metabolism*. The way the brain responds to hormones indicates that the brain is very malleable and capable of responding to environmental signals.

The brain contains receptors for thyroid hormones (those produced by the thyroid) and the six classes of steroid hormones, which are synthesized from cholesterol — *androgens*, *estrogens*, *progestins*, *glucocorticoids*, mineralocorticoids, and vitamin D. The receptors are found in selected populations of neurons in the brain and relevant organs in the body. Thyroid and steroid hormones bind to receptor proteins that in turn bind to DNA and regulate the action of genes. This can result in long-lasting changes in cellular structure and function.

The brain has receptors for many hormones; for example, the metabolic hormones insulin, insulin-like growth factor, ghrelin, and leptin. These hormones are taken up from the blood and act to affect neuronal activity and certain aspects of neuronal structure.

In response to stress and changes in our biological clocks, such as day and night cycles and jet lag, hormones enter the blood and travel to the brain and other organs. In the brain, hormones alter the production of gene products that participate in synaptic neurotransmission as well as affect the structure of brain cells. As a result, the circuitry of the brain and its capacity for neurotransmission are changed over a course of hours to days. In this way, the brain adjusts its performance and control of behavior in response to a changing environment.

Hormones are important agents of protection and adaptation, but stress and stress hormones, such as the glucocorticoid *cortisol*, can also alter brain function, including the brain's capacity to learn. Severe and prolonged stress can impair the ability of the brain to function normally for a period of time, but the brain is also capable of remarkable recovery.

Reproduction in females is a good example of a regular, cyclic process driven by circulating hormones and involving a feedback loop: The neurons in the hypothalamus produce gonadotropin-releasing hormone (GnRH), a peptide that acts on cells in the pituitary. In both males and females, this causes two hormones — the *follicle-stimulating hormone* (FSH) and the luteinizing hormone (LH) — to be released into the bloodstream. In females, these hormones act on the ovary to stimulate ovulation and promote release of the ovarian hormones estradiol and progesterone. In males, these hormones are carried to receptors on cells in the testes, where they promote spermatogenesis and release the male hormone testosterone, an androgen, into the bloodstream. Testosterone, estrogen, and progesterone are often referred to as sex hormones.

In turn, the increased levels of testosterone in males and estrogen in females act on the hypothalamus and pituitary to decrease the release of FSH and LH. The increased levels of sex hormones also induce changes in cell structure and chemistry, leading to an increased capacity to engage in sexual behavior. Sex hormones also exert widespread effects on many other functions of the brain, such as attention, motor control, pain, mood, and memory.

Sexual differentiation of the brain is caused by sex hormones acting in fetal and early postnatal life, although recent evidence suggests genes on either the X or Y chromosome may also contribute to this process. Scientists have found statistically and biologically significant differences between the brains of men and women that are similar to sex differences found in experimental animals. These include differences in the size and shape of brain structures in the hypothalamus and the arrangement of neurons in the cortex and hippocampus. Sex differences go well beyond sexual behavior and reproduction and affect many brain regions and functions, ranging from mechanisms for perceiving pain and dealing with stress to strategies for solving cognitive problems. That said, however, the brains of men and women are more similar than they are different.

Anatomical differences have also been reported between the brains of heterosexual and homosexual men. Research suggests that hormones and genes act early in life to shape the brain in terms of sex-related differences in structure and function, but scientists are still putting together all the pieces of this puzzle.

Gases and Other Unusual Neurotransmitters

Scientists have identified a new class of neurotransmitters that are gases. These molecules — nitric oxide and carbon monoxide — do not act like other neurotransmitters. Being gases, they are not stored in any structure, certainly not in storage structures for classical and peptide transmitters. Instead, they are made by enzymes as they are needed and released from neurons by diffusion. Rather than acting at receptor sites, these gases simply diffuse into adjacent neurons and act upon chemical targets, which may be enzymes.

Working in tandem with the rest of the nervous system, the brain sends and receives messages, allowing for ongoing communication.

Although exact functions for carbon monoxide have not been determined, nitric oxide has already been shown to play several important roles. For example, nitric oxide neurotransmission governs erection in the penis. In nerves of the intestine, it governs the relaxation that contributes to the normal movements of digestion. In the brain, nitric oxide is the major regulator of the intracellular messenger molecule cyclic GMP. In conditions of excess glutamate release, as occurs in stroke, neuronal damage following the stroke may be attributable in part to nitric oxide.

Lipid Messengers In addition to gases, which act rapidly, the brain also derives signals from lipids. Prostaglandins are a class of compounds made from lipids by an enzyme called cyclooxygenase. These very small and short-lived molecules have powerful effects, including the induction of a fever and the generation of pain in response to inflammation. Aspirin reduces a fever and lowers pain by inhibiting the cyclooxygenase enzyme. A second class of membrane-derived messenger is the brain's own marijuana, referred to as *endocannabinoids*, because they are in essence cannabis made by the brain. These messengers control the release of neurotransmitters, usually by inhibiting them, and can also affect the immune system and other cellular parameters still being discovered. Endocannabinoids play an important role in the control of behaviors. They increase in the brain under stressful conditions.

Second Messengers After the action of neurotransmitters at their receptors, biochemical communication within cells is still possible. Substances that trigger such communication are called *second messengers*. Second messengers convey the chemical message of a neurotransmitter (the first messenger) from the cell membrane to the cell's internal biochemical machinery. Second messenger effects may endure for a few milliseconds to as long as many minutes. They also may be responsible for long-term changes in the nervous system.

An example of the initial step in the activation of a second messenger system involves adenosine triphosphate (ATP), the chemical source of energy in cells. ATP is present throughout the cytoplasm of all cells. For example, when norepinephrine binds to its receptors on the surface of the neuron, the activated receptor binds a G protein on the inside of the membrane. The activated G protein causes the enzyme adenylyl cyclase to convert ATP to cyclic adenosine monophosphate (cAMP), the second messenger. Rather than acting as a messenger between one neuron and another, cAMP exerts a variety of influences within the cell, ranging from changes in the function of ion channels in the membrane to changes in the expression of genes in the nucleus.

Second messengers also are thought to play a role in the manufacture and release of neurotransmitters and in intracellular movements and carbohydrate metabolism in the cerebrum — the largest part of the brain, consisting of two hemispheres. Second messengers also are involved in growth and development processes. In addition, the direct effects of second messengers on the genetic material of cells may lead to long-term alterations in cellular functioning and, ultimately, to changes in behavior.

The intricate communication systems in the brain and the nervous system begin to develop about three weeks after gestation. How this process unfolds and how it is relevant to an understanding of brain-based conditions and illnesses are discussed in Chapter 2.

Chapter 2: The Developing Brain

In this Chapter

- The Journey of Nerve Cells
- Critical Periods
- Plasticity

The amazing capabilities of the human brain arise from exquisitely intricate communication among its billions of interacting brain cells. Although the specific patterns of connectivity are forged by the ever-changing interplay between a person's genes and his specific environment, much of the development of brain cells occurs during the prenatal period. Understanding the processes underlying how brain cells are formed, become specialized, travel to their appropriate location, and connect to each other in increasingly elaborate adaptive networks is the central challenge of developmental neurobiology.

Advances in the study of brain development have become increasingly relevant for medical treatments. For example, several diseases that most scientists once thought were purely disorders of adult function, such as schizophrenia, are now being considered in developmental terms; that is, such disorders may occur because pathways and connections to the brain did not form correctly early in life. Other research suggests that genes important for brain development may also play a role in susceptibility to *autism spectrum disorders*. And by applying knowledge about how connections form during development, regeneration following injury to the brain is now viewed as a future possibility.

Knowing how the brain is constructed is essential for understanding its ability to reorganize in response to external influences or injury. As the brain evolves from the embryo to the adult stage, unique attributes evolve during infancy and childhood that contribute to differences in learning ability as well as vulnerability to specific brain disorders. Neuroscientists are beginning to discover some general principles that underlie developmental processes, many of which overlap in time.

The Journey of Nerve Cells

The development of neurons occurs through a delicate process. Signaling molecules "turn on" certain genes and "turn off" others, beginning the process of nerve cell induction. Even more astonishing is that this process takes place as the embryo is developing. Induction and proliferation are followed by *migration*, during which the newly formed neurons travel to their final destination. Throughout life, the nervous system is active, making new connections and fine-tuning the way messages are sent and received. The activities of the ever-changing nervous system are explained in more detail in the following sections.

Induction

During the early stages of embryonic development, three layers emerge — the endoderm, the ectoderm, and the mesoderm. These layers undergo many interactions to grow into organ, bone, muscle, skin, or nerve tissue. How does this process of differentiation occur, especially since each cell contains 25,000 genes, the entire sequence of DNA instructions for development? The answer lies in signaling molecules released by the mesoderm. These molecules turn on certain genes and turn off others, triggering some ectoderm cells to become nerve tissue in a process called *neural induction*. Subsequent signaling interactions further refine the nerve tissue into the basic categories of neurons or glia (support cells), then into subclasses of each cell type. The remaining cells of the ectoderm, which have not received the signaling molecules diffusing from the mesoderm, become skin.

The proximity of cells to the signaling molecules largely determines their fate. That's because the concentration of these molecules spreads out and weakens the farther it moves from its source. For example, a particular signaling molecule, called sonic hedgehog, is secreted from mesodermal tissue lying beneath the developing spinal cord. As a result, the adjacent nerve cells are converted into a specialized class of glia. Cells that are farther away, however, are exposed to lower concentrations of sonic hedgehog, so they become the *motor neurons* that control muscles. An even lower concentration promotes the formation of *interneurons*, which relay messages to other neurons, not muscles. Interestingly, the mechanism of

The human brain and nervous system begin to develop at about three weeks' gestation with the closing of the neural tube (left image). By four weeks, major regions of the human brain can be recognized in primitive form, including the forebrain, midbrain, hindbrain, and optic vesicle, from which the eye develops. Ridges, or convolutions, can be seen by six months.

this basic signaling molecule is very similar in species as diverse as flies and humans.

Migration Once neural induction has occurred, the next step for new neurons is a journey to the proper position in the brain. This process is called migration, and it begins three to four weeks after a human baby is conceived. At this time, the ectoderm starts to thicken and build up along the middle. As the cells continue to divide, a flat neural plate grows, followed by the formation of parallel ridges, similar to the creases in a paper airplane, that rise across its surface. Within a few days, the ridges fold in toward each other and fuse to form a hollow neural tube. The top of the tube thickens into three bulges that form the hindbrain, the midbrain, and the forebrain. Later in the process, at week seven, the first signs of the eyes and the brain's hemispheres appear. As neurons are produced, they move from the neural tube's ventricular zone, or inner surface, to near the border of the marginal zone, or outer surface.

After neurons stop dividing, they form an intermediate zone, where they gradually accumulate as the brain develops. The neurons then migrate to their final destination— with the help of a variety of guidance mechanisms. The most common guidance mechanism, accounting for about 90 percent of migration in humans, are glia, which project radially from the intermediate zone to the cortex. In this way, glia provide a temporary scaffolding for ushering neurons to their destination. This process of radial migration occurs in an "inside-out" manner; that is, the cells that arrive the earliest (the oldest ones) form the deepest layer of the cortex, whereas the late-arriving (the youngest) neurons form the outermost layer. Through another mechanism, inhibitory interneurons, small neurons with short pathways usually found in the central nervous system, migrate tangentially across the brain.

Migration is a delicate process and can be affected by different factors. External forces, such as alcohol, cocaine, or radiation, can prevent proper migration, resulting in misplacement of cells, which may lead to mental retardation or *epilepsy*. Furthermore, *mutations* in genes that regulate migration have been shown to cause some rare genetic forms of retardation and epilepsy in humans.

Making Connections Once the neurons reach their final location, they must make the proper connections so that a particular function, such as vision or hearing, can emerge. Unlike induction, proliferation, and migration, which occur internally during fetal development, the next phases of brain development are increasingly dependent on interactions with the environment. After birth and beyond, such activities as listening to a voice, responding to a toy, and even the reaction evoked by the temperature in the room lead to more connections among neurons.

Neurons become interconnected through (1) the growth of dendrites — extensions of the cell body that receive signals from other neurons and (2) the growth of axons — extensions from the neuron that can carry signals to other neurons. Axons enable connections between neurons at considerable distances, sometimes at the opposite side of the brain, to develop. In the case of motor neurons, the axon may travel from the spinal cord all the way down to a foot muscle.

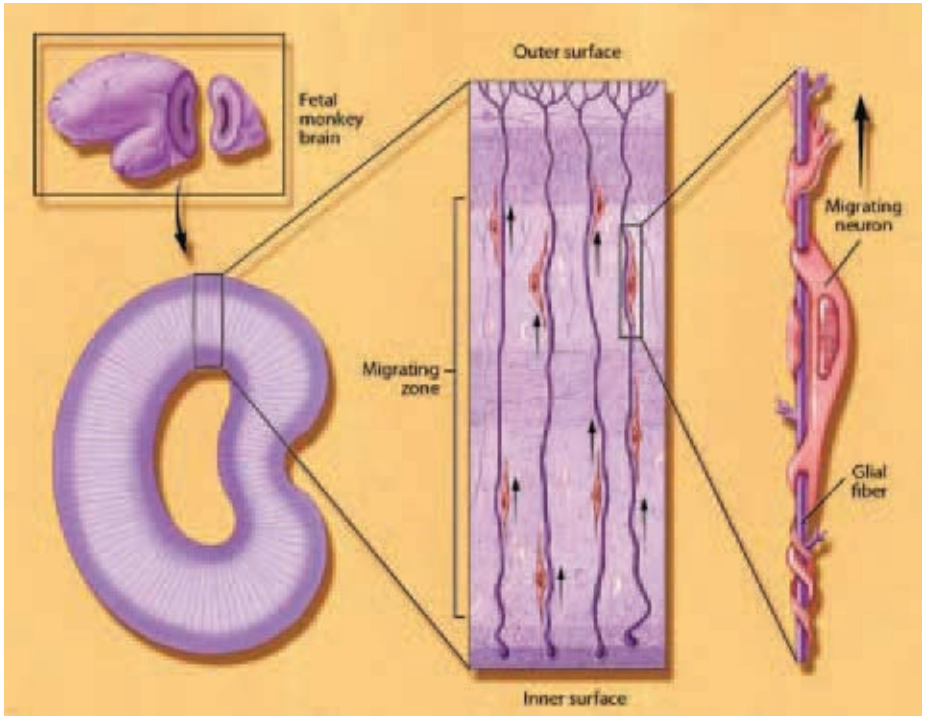
Growth cones, enlargements on the axon's tip, actively explore the environment as they seek out their precise destination. Researchers have discovered many special molecules that help guide growth cones. Some molecules lie on the cells that growth cones contact, whereas others are released from sources found near the growth cone. The growth cones, in turn, bear molecules that serve as receptors for the environmental cues. The binding of particular signals with receptors tells the growth cone whether to move forward, stop, recoil, or change direction. These signaling molecules include proteins with names such as netrin, semaphorin, and ephrin. In most cases, these are families of related molecules; for example, researchers have identified at least fifteen semaphorins and at least nine ephrins.

Perhaps the most remarkable finding is that most of these proteins are common to many organisms—worms, insects, and mammals, including humans. Each protein family is smaller in flies or worms than in mice or people, but its functions are quite similar. As a result, it has been possible to use the simpler animals as experimental models to gain knowledge that can be applied directly to humans. For example, the first netrin was discovered in a worm and shown to guide neurons around the worm's "nerve ring." Later, vertebrate netrins were found to guide axons around the mammalian spinal cord. Receptors for netrins were then found in worms, a discovery that proved to be invaluable in finding the corresponding, and related, human receptors.

Once axons reach their targets, they form connections with other cells at synapses. At the synapse, the electrical signal of the sending axon is transmitted by chemical neurotransmitters to the receiving dendrites of another neuron, where they can either provoke or prevent the generation of a new signal. The regulation of this transmission at synapses and the integration of inputs from the thousands of synapses each neuron receives are responsible for the astounding information-processing capacity of the brain.

For processing to occur properly, the connections must be highly specific. Some specificity arises from the mechanisms that guide each axon to its proper target area. Additional molecules mediate target recognition when the axon chooses the proper neuron. They often also mediate the proper part of the target once the axon arrives at its destination. Over the past few years, several of these recognition molecules have been identified. Dendrites also are actively involved in the process of initiating contact with axons and recruiting proteins to the "postsynaptic" side of the synapse.

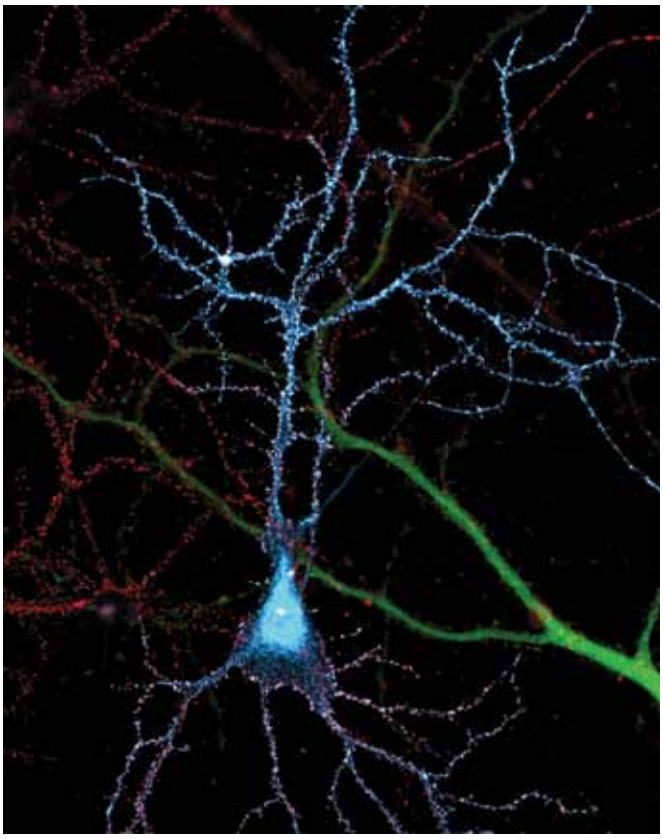
Researchers have successfully identified ways in which the synapse differentiates once contact has been made. The tiny portion of the axon that contacts the dendrite becomes specialized for the release of neurotransmitters, and the tiny portion of the dendrite that receives the contact becomes specialized to receive and respond to the signal. Special molecules pass between the sending and receiving cells to ensure that the contact is formed properly and that the sending and receiving specializations are matched precisely. These processes ensure that the synapse can transmit signals quickly and effectively. Finally, still other molecules coordinate the maturation of the synapse after it has formed so that it can accommodate the changes that occur as our bodies mature and our behavior changes. Defects in some



This is a cross-sectional view of the occipital lobe, which processes vision, of a three-month-old monkey fetus brain. The center shows immature neurons migrating along glial fibers. These neurons make transient connections with other neurons before reaching their destination. A single migrating neuron, shown about 2,500 times its actual size (right), uses a glial fiber as a guiding scaffold.

of these molecules are now thought to make people susceptible to disorders such as autism. The loss of other molecules may underlie the degradation of synapses that occurs during aging.

A combination of signals also determines the type of neurotransmitters that a neuron will use to communicate with other cells. For some cells, such as motor neurons, the type of neurotransmitter is fixed, but for other neurons, it is not. Scientists found that when certain immature neurons are maintained in a dish with no other cell types, they produce the neurotransmitter norepinephrine. In contrast, if the same neurons are maintained with specific cells, such as cardiac, or heart, tissue, they produce the neurotransmitter acetylcholine. Just as genes turn on and off signals to regulate the development of specialized cells, a similar process leads to the production of specific neurotransmitters. Many researchers believe that the signal to engage the gene, and therefore the final determination of the chemical messengers that a neuron produces, is influenced by factors coming from the location of the synapse itself.



Neurons communicate with electrical and chemical signals at special contact points called synapses. [Credit: Meagan A. Jenkins, et al., *The Journal of Neuroscience* 2010, 30(15): 5125-5135]

Myelination Insulation covering wires preserves the strength of the electrical signals that travel through them. The myelin sheath covering axons serves a similar purpose. Myelination, the wrapping of axons by extensions of glia, increases the speed at which signals may be sent from one neuron to another by a factor of up to 100x. This advantage is due to how the sheath is wrapped. In between the myelin are gaps, called nodes of Ranvier, that are not covered in myelin. The electrical signal moves faster over the insulated portion, jumping from one node to another. This phenomenon, known as saltatory conduction (the word "saltatory" means "to jump"), is responsible for the rapid transmission of electrical signals. The process of myelination occurs throughout the lifespan.

Paring Back After growth, the neural network is pared back to create a more efficient system. Only about half the neurons generated during development survive to function in the adult. Entire populations of neurons are removed through *apoptosis*, programmed cell death initiated in the cells. Apoptosis is activated if a neuron loses its battle with other neurons to receive life-sustaining chemical signals called trophic factors. These factors are produced in limited quantities by target tissues. Each type of trophic factor supports the survival of a distinct group of neurons. For example, *nerve growth factor* is important for sensory neuron survival. Recently, it has become clear that apoptosis is maintained into adulthood and constantly held in check. On the basis of this idea, researchers have found that injuries and some neurodegenerative diseases kill neurons not by directly inflicting damage but rather by activating the cells' own death programs. This discovery — and its implication that death need not follow insult — have led to new avenues for therapy.

Brain cells also form excess connections at first. For example, in primates, the projections from the two eyes to the brain initially overlap and then sort out to separate territories devoted to one eye or the other. Furthermore, in the young primate cerebral cortex, the connections between neurons are greater in number and twice as dense as those in an adult primate. Communication between neurons with chemical and electrical signals is necessary to weed out the connections. The connections that are active and generating electrical currents survive, whereas those with little or no activity are lost. Thus, the circuits of the adult brain are formed, at least in part, by sculpting away incorrect connections to leave only the correct ones.

Critical Periods

Genes and the environment converge powerfully during early sensitive windows of brain development to form the neural circuits underlying behavior. Although most neuronal cell death occurs in the embryo, the paring down of connections occurs in large part during critical periods in early postnatal life. During these moments in time, the developing nervous system must obtain certain critical experiences, such as sensory, movement, or emotional input, to mature properly. Such periods are characterized by high learning rates as well as enduring consequences for neuronal connectivity.

After a critical period, connections diminish in number and are less subject to change, but the ones that remain are stronger, more reliable, and more precise. These turn into the unique variety of sensory, motor, or cognitive "maps" that best reflect our world. It is important to note that there are multiple critical periods, organized sequentially, as individual brain functions are established. The last step in the creation of an adult human brain, the frontal lobes, whose function includes judgment, insight, and impulse control, continues into the early 20s. Thus, even the brain of an adolescent is not completely mature.

Injury or deprivation of environmental input occurring at specific stages of postnatal life can dramatically reshape the underlying circuit development, which becomes increasingly more difficult to correct later in life. In one experiment, a monkey raised from birth to 6 months of age with one eyelid closed permanently lost useful vision in that eye because of diminished use. This gives cellular meaning to the saying "use it or lose it." Loss of vision is caused by the actual loss of functional connections between that eye and neurons in the visual cortex. This finding has led to earlier and better treatment for the eye disorders of congenital cataracts and "lazy eye" in children. Similarly, cochlear implants introduced in infancy are most effective in restoring hearing to the congenitally deaf. Cognitive recovery from social deprivation, brain damage, or stroke is also greatest early in life. Conversely, research suggests that enriched environments or stimulation may bolster brain development, as revealed by animals raised in toy-filled surroundings. They have more branches on their neurons and more connections than isolated animals.

Many people have observed that children can learn languages or develop musical ability (absolute pitch) with greater proficiency than adults. Heightened activity in the critical period may, however, also contribute to an increased incidence of certain disorders in childhood, such as epilepsy. Fortunately, as brain activity subsides, many types of epilepsy fade away by adulthood.

Plasticity

The ability of the brain to modify itself and adapt to challenges of the environment is referred to as plasticity. Plasticity itself is not unique to humans, but the degree to which our brains are able to adapt is the defining attribute of our species. Plasticity can be categorized as experience-expectant or experience-dependent.

Experience-expectant plasticity refers to the integration of environmental stimuli into the normal patterns of development. Certain environmental exposures during limited critical, or sensitive, periods of development are essential for healthy maturation. For example, finches need to hear adult songs before sexual maturation in order for them to learn to sing at a species-appropriate level of intricacy.

Scientists hope that new insight into brain development will lead to treatments for those with learning disabilities, brain damage, and neurodegenerative disorders, as well as help us understand aging. If we can figure out a way to lift the brakes that restrict adult plasticity — either pharmacologically or by circuit rewiring — it may be possible to correct damage done through mistimed critical periods or other means. By understanding normal functions of the brain during each developmental stage, researchers hope to develop better age-specific therapies for brain disorders.

This chapter discussed how cells differentiate so that they can perform specific functions, such as seeing and hearing. Those are just two of the senses we rely on to learn about the world. The senses of taste, smell, and touch also provide key information. Through intricate systems and networks, the brain and the nervous system work together to process these sensory inputs. Part 2, called Sensing, Thinking, and Behaving, describes how these systems work and complement each other. It begins with a look at senses and perception.

Chapter 3: Senses and Perception

In this Chapter

- Vision
- Hearing
- Taste and Smell
- Touch and Pain

Vision

The wonderful sense of sight allows us to experience the world, from the genius of Michelangelo's Sistine Chapel ceiling to the mist-filled vista of a mountain range. Vision is one of our most delicate and complicated senses. Many processes must occur simultaneously in order for us to see what is happening around us. Information about image size and shape, color, motion, and location in space all must be gathered, encoded, integrated, and processed. Performing these activities involves about 30 percent of the human brain — more than for any other sense.

Vision has been studied intensively. As a result, neuroscientists may know more about it than any other sensory system. Most information about initial stages of visual transduction, or how light is converted into electrical signals, comes from studies of *Drosophila* (fruit flies) and mice, whereas visual processing has been mostly studied in monkeys and cats.

It all Starts with Light

Vision begins with light passing through the cornea, which does about three-quarters of the focusing, and then the lens, which adjusts the focus. Both combine to produce a clear image of the visual world on a sheet of *photoreceptors* called the *retina*, which is part of the central nervous system but located at the back of the eye.

Photoreceptors gather visual information by absorbing light and sending electrical signals to other retinal neurons for initial processing and integration. The signals are then sent via the optic nerve to other parts of brain, which ultimately processes the image and allows us to see.

As in a camera, the image on the retina is reversed: Objects to the right of center project images to the left part of the retina and vice versa; objects above the center project to the lower part and vice versa. The size of the pupil, which regulates how much light enters the eye, is controlled by the iris. The shape of the lens is altered by the muscles just behind the iris so that near or far objects can be brought into focus on the retina.

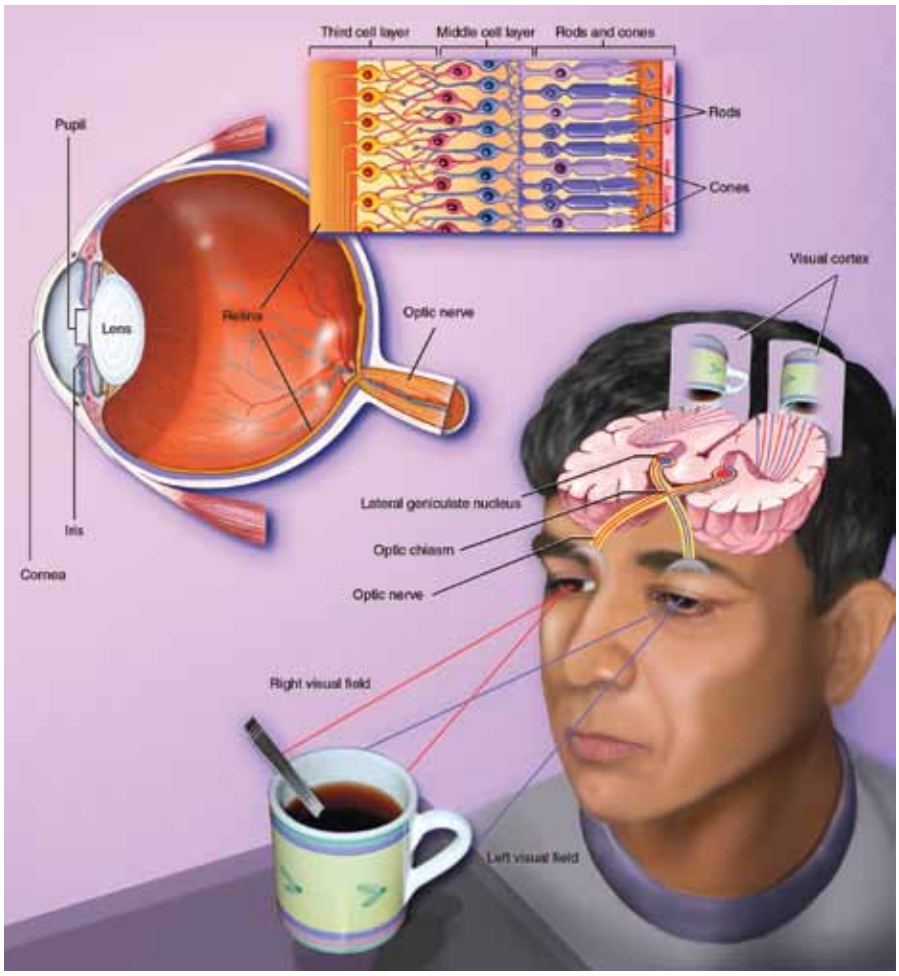
Primates, including humans, have well-developed vision using two eyes, called binocular vision. Visual signals pass from each eye along the million or so fibers of the optic nerve to the optic chiasm, where some nerve fibers cross over. This crossover allows both sides of the brain to receive signals from both eyes.

When you look at a scene with both eyes, the objects to your left register on the right side of the retina. This visual information then maps to the right side of the cortex. The result is that the left half of the scene you are watching registers in the cerebrum's right hemisphere. Conversely, the right half of the scene registers in the cerebrum's left hemisphere. A similar arrangement applies to movement and touch: Each half of the cerebrum is responsible for processing information received from the opposite half of the body.

Scientists know much about the way cells encode visual information in the retina, but relatively less about the lateral geniculate nucleus — an intermediate way station between the retina and visual cortex — and the visual cortex. Studies about the inner workings of the retina give us the best knowledge we have to date about how the brain analyzes and processes sensory information.

Photoreceptors, about 125 million in each human eye, are neurons specialized to turn light into electrical signals. Two major types of photoreceptors are *rods* and *cones*. Rods are extremely sensitive to light and allow us to see in dim light, but they do not convey color. Rods constitute 95 percent of all photoreceptors in humans. Most of our vision, however, comes from cones that work under most light conditions and are responsible for acute detail and color vision.

The human eye contains three types of cones (red, green and blue), each sensitive to a different range of colors. Because their sensitivities overlap, cones work in combination to convey information about all visible colors. You might be surprised to know that we can see thousands of colors using only three types of cones, but computer monitors use a similar



Vision begins with light passing through the cornea and the lens, which combine to produce a clear image of the visual world on a sheet of photoreceptors called the retina. As in a camera, the image on the retina is reversed: Objects above the center project to the lower part and vice versa. The information from the retina — in the form of electrical signals — is sent via the optic nerve to other parts of the brain, which ultimately process the image and allow us to see.

process to generate a spectrum of colors. The central part of the human retina, where light is focused, is called the *fovea*, which contains only red and green cones. The area around the fovea, called the macula, is critical for reading and driving. Death of photoreceptors in the macula, called macular degeneration, is a leading cause of blindness among the elderly population in developed countries, including the United States.

The retina contains three organized layers of neurons. The rod and cone photoreceptors in the first layer send signals to the middle layer (interneurons), which then relays signals to the third layer, consisting of multiple different types of ganglion cells, specialized neurons near the inner surface of the retina. The axons of the ganglion cells form the optic nerve. Each neuron in the middle and third layer typically receives input from many cells in the previous layer, and the number of inputs varies widely across the retina. Near the center of the gaze, where visual acuity is highest, each ganglion cell receives inputs — via the middle layer — from one cone or, at most, a few, allowing us to resolve very fine details. Near the margins of the retina, each ganglion cell receives signals from many rods and cones, explaining why we cannot see fine details on either side. Whether large or small, the region of visual space providing input to a visual neuron is called its receptive field.

How Visual Information Is Processed

About 60 years ago, scientists discovered that each vision cell's receptive field is activated when light hits a tiny region in the center of the field and inhibited when light hits the area surrounding the center. If light covers the entire receptive field, the cell responds weakly. Thus, the visual process begins by comparing the amount of light striking any small region of the retina with the amount of surrounding light.

Visual information from the retina is relayed through the lateral geniculate nucleus of the thalamus to the primary visual cortex — a thin sheet of tissue (less than one-tenth of an inch thick), a bit larger than a half-dollar, which is located in the occipital lobe in the back of the brain. The primary visual cortex is densely packed with cells in many layers, just as the retina is. In its middle layer, which receives messages from the lateral geniculate nucleus, scientists have found responses similar to those seen in the retina and in lateral geniculate cells. Cells above and below this layer respond differently. They prefer stimuli in the shape of bars or edges and those at a particular angle (orientation). Further studies have shown that different cells prefer edges at different angles or edges moving in a particular direction.

Although the visual processing mechanisms are not yet completely understood, recent findings from anatomical and physiological studies in monkeys suggest that visual

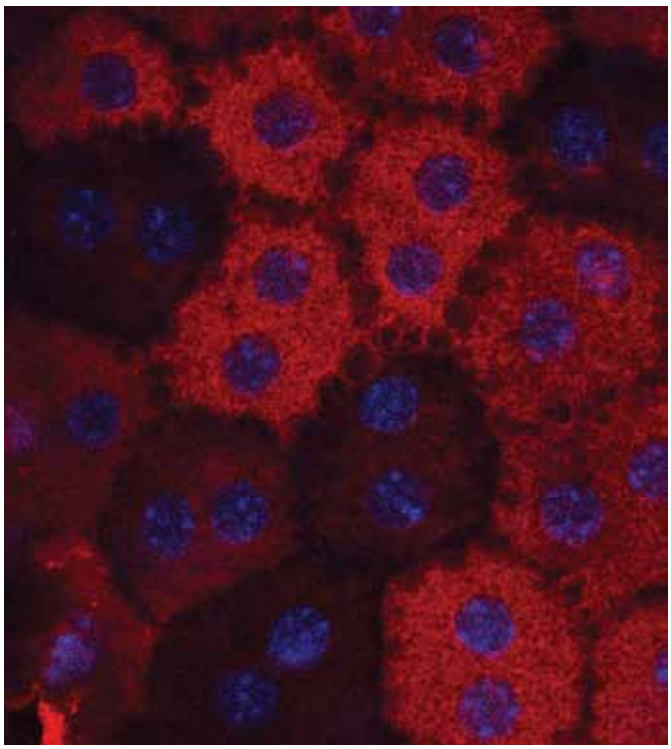
signals are fed into at least three separate processing systems. One system appears to process information mainly about shape; a second, mainly about color; and a third, movement, location, and spatial organization. Human psychological studies support the findings obtained through animal research. These studies show that the perception of movement, depth, perspective, the relative size of objects, the relative movement of objects, shading, and gradations in texture all depend primarily on contrasts in light intensity rather than on color. Perception requires various elements to be organized so that related ones are grouped together. This stems from the brain's ability to group the parts of an image together and also to separate images from one another and from their individual backgrounds.

How do all these systems combine to produce the vivid images of solid objects that we perceive? The brain extracts biologically relevant information at each stage and associates firing patterns of neuronal populations with past experience.

Research Leads to More Effective Treatment

Vision studies also have led to better treatment for visual disorders. Information from research in cats and monkeys has improved the therapy for strabismus, a condition in which the eyes are not properly aligned with each other and point in different directions. It is also termed squint, cross-eye, or walleye. Children with strabismus initially have good vision in each eye. But because they cannot fuse the images in the two eyes, they tend to favor one eye and often lose useful vision in the other. Vision can be restored in such cases, but only during infancy or early childhood. Beyond the age of 8 or so, the blindness in one eye becomes permanent. Until a few decades ago, ophthalmologists waited until children reached the age of 4 before operating to align the eyes, prescribing exercises, or using an eye patch. Now strabismus is corrected very early in life — before age 4 — when normal vision can still be restored.

Extensive genetic studies and use of model organisms have allowed us to identify defects in inherited eye diseases, making it possible to design gene or stem cell-based therapy and discover new drugs for treatment. Loss of function or death of photoreceptors appears to be a major cause of blindness in many diseases that are currently incurable. Recently, gene therapy for a small group of patients with severe blindness allowed them to see. Work also is in progress to bypass lost photoreceptors and send electrical signals directly to the brain via ganglion cells.



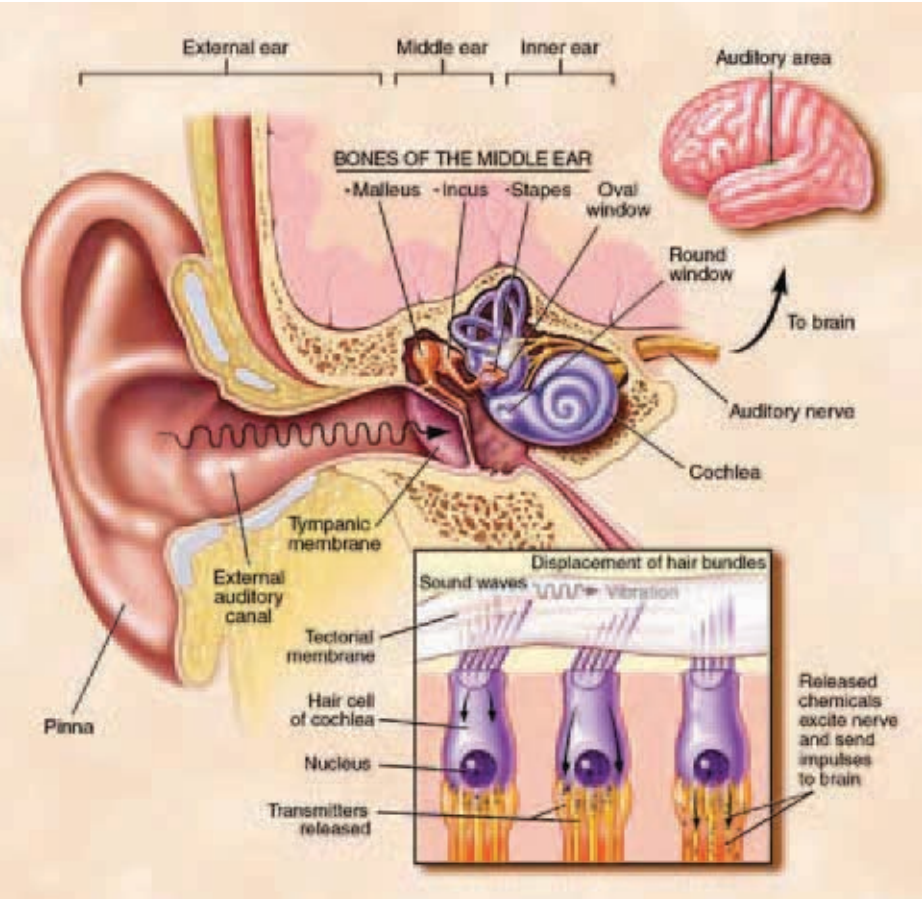
Mutations in the RPE65 protein (labeled in retinal cells in red) cause an inherited form of blindness that may be corrected by gene therapy. [Credit: National Eye Institute, National Institutes of Health]

Hearing

Often considered the most important sense for humans, hearing allows us to communicate with each other by receiving sounds and interpreting speech. Hearing also gives information vital to survival; for instance, by alerting us to an approaching car, it enables us to get out of harm's way.

Like the visual system, our hearing system picks up several qualities in the signals it detects (for example, a sound's location, its loudness, and its pitch). Our hearing system does not blend the frequencies of different sounds, as the visual system does when different wavelengths of light are mixed to produce color. Instead, it separates complex sounds into their component tones or frequencies so that we can follow different voices or instruments as we listen to conversations or to music.

Whether from the chirping of crickets or the roar of a rocket engine, sound waves are collected by the external ear — the pinna and the external auditory canal — and funneled to the tympanic membrane (eardrum) to make it vibrate. Attached to the tympanic membrane, the malleus (hammer) transmits the vibration to the incus (anvil), which passes the vibration on to the stapes (stirrup). The stapes pushes on the oval window, which separates the air-filled middle ear from the



Sound waves are collected by the external ear — the pinna and the external auditory canal — and funneled to the tympanic membrane (eardrum) to make it vibrate. Attached to the tympanic membrane, the malleus (hammer) transmits the vibration to the incus (anvil), which passes the vibration on to the stapes (stirrup). Hair cells convert the mechanical vibration to electrical signals, which in turn excite the 30,000 fibers of the auditory nerve. The auditory nerve then carries the signals to the brainstem. From there, nerve fibers send the information to the auditory cortex, the part of the brain involved in perceiving sound.

fluid-filled inner ear to produce pressure waves in the inner ear's snail-shaped *cochlea*. The separation of frequencies occurs in the cochlea, which is tuned along its length to different frequencies, so that a high note causes one region of the cochlea's basilar membrane to vibrate, while a lower note has the same effect on a different region of the basilar membrane.

Riding on the vibrating basilar membrane are *hair cells* topped with microscopic bundles of hairlike stereocilia, which are deflected by the overlying tectorial membrane. Hair cells convert the mechanical vibration to electrical signals, which in turn excite the 30,000 fibers of the *auditory nerve*. The auditory nerve then carries the signals to the brainstem. Because each hair cell rides on a different part of the basilar membrane, each responds to a different frequency. As a result, each nerve fiber carries information about a different frequency to the brain. Auditory information is analyzed by multiple brain centers as it flows to the superior temporal gyrus, or auditory cortex, the part of the brain involved in perceiving sound.

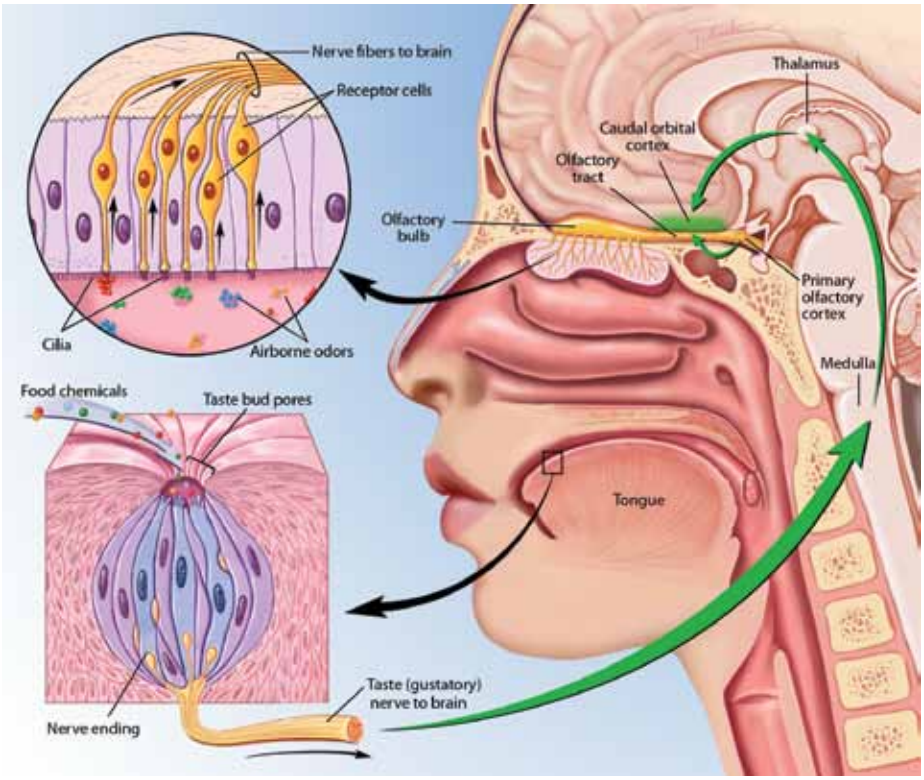
In the auditory cortex, adjacent neurons tend to respond to tones of similar frequency. However, they specialize in different combinations of tones. Some respond to pure tones, such as those produced by a flute, and some to complex sounds like those made by a violin. Some respond to long sounds and some to short, and some to sounds that rise or fall in frequency. Other neurons might combine information from these specialist neurons to recognize a word or an instrument.

Sound is processed in different regions of the auditory cortex on both sides of the brain. However, for most people, the left side is specialized for perceiving and producing speech. Damage to the left auditory cortex, such as from a stroke, can leave someone able to hear but unable to understand language.

Taste and Smell

Although most of us don't think of it in this way, the related senses of taste and smell help us interpret the chemical world. Just as sound is the perception of changes in air pressure and sight the perception of light, tastes and smells are the perception of chemicals in the air or in our food. Separate senses with their own receptor organs, taste and smell are nonetheless intimately entwined.

This close relationship is most apparent in how we perceive the flavors of food. As anyone with a head cold



Taste and smell are separate senses with their own receptor organs, yet they are intimately entwined. Tastants, chemicals in foods, are detected by taste buds, which consist of special sensory cells. When stimulated, these cells send signals to specific areas of the brain, which make us conscious of the perception of taste. Similarly, specialized cells in the nose pick up odorants, airborne odor molecules. Odorants stimulate receptor proteins found on hairlike cilia at the tips of the sensory cells, a process that initiates a neural response. Ultimately, messages about taste and smell converge, allowing us to detect the flavors of food.

can attest, food "tastes" different when the sense of smell is impaired. Actually, what is really being affected is the flavor of the food, or the combination of taste and smell. That's because only the taste, not the food odors, are being detected. Taste itself is focused on distinguishing chemicals that have a sweet, salty, sour, bitter, or umami taste (umami is Japanese for "savory"). However, interactions between the senses of taste and smell enhance our perceptions of the foods we eat.

Tastants, chemicals in foods, are detected by *taste buds*, special structures embedded within small protuberances on the tongue called papillae. Other taste buds are found in the back of the mouth and on the palate. Every person has between 5,000 and 10,000 taste buds. Each taste bud consists of 50 to 100 specialized sensory cells, which are stimulated by tastants such as sugars, salts, or acids. When the sensory cells are stimulated, they cause signals to be transferred to the ends of nerve fibers, which send impulses along *cranial nerves* to taste regions in the brainstem. From here, the impulses are relayed to the thalamus and on to a specific area of the cerebral cortex, which makes us conscious of the perception of taste.

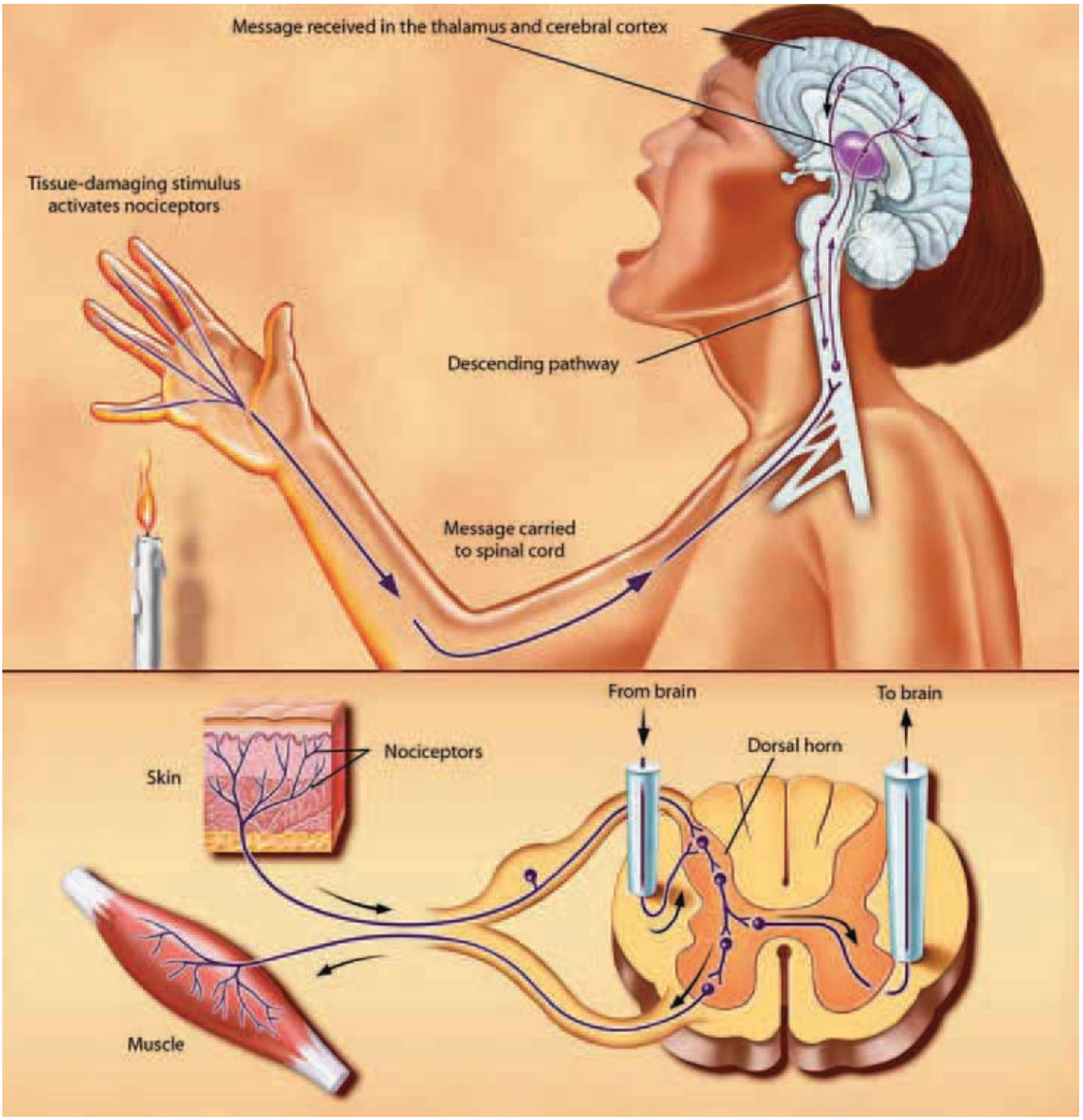
Airborne odor molecules, called odorants, are detected by specialized sensory neurons located in a small patch of mucus membrane lining the roof of the nose. Axons of these sensory cells pass through perforations in the overlying bone and enter two elongated *olfactory bulbs* lying against the underside of the frontal lobe of the brain.

Odorants stimulate receptor proteins found on hairlike cilia at the tips of the sensory cells, a process that initiates a neural response. An odorant acts on more than one receptor, but does so to varying degrees. Similarly, a single receptor interacts with more than one different odorant, though also to varying degrees. Therefore, each odorant has its own pattern of activity, which is set up in the sensory neurons. This pattern of activity is then sent to the olfactory bulb, where other neurons are activated to form a spatial map of the odor. Neural activity created by this stimulation passes to the primary olfactory cortex at the back of the underside, or orbital, part of the frontal lobe. Olfactory information then passes to adjacent parts of the orbital cortex, where the combination of odor and taste information helps create the perception of flavor.

Touch and Pain

Touch is the sense by which we determine the characteristics of objects: size, shape, and texture. We do this through touch receptors in the skin. In hairy skin areas, some receptors consist of webs of sensory nerve cell endings wrapped around the base of hairs. The nerve endings are remarkably sensitive. They can be triggered by the slightest movement of the hairs.

Signals from touch receptors pass via sensory nerves to the spinal cord, where they synapse, or make contact with, other nerve cells, which in turn send the information to the thalamus and sensory cortex. The transmission of this information is highly topographic, meaning that the body



Pain messages are picked up by receptors and transmitted to the spinal cord via small myelinated fibers and very small unmyelinated fibers. From the spinal cord, the impulses are carried to the brainstem, thalamus, and cerebral cortex and ultimately perceived as pain. These messages can be suppressed by a system of neurons that originates in the midbrain. This descending pathway sends messages to the spinal cord where it suppresses the transmission of tissue damage signals to the higher brain centers.

is represented in an orderly fashion at different levels of the nervous system. Larger areas of the cortex are devoted to sensations from the hands and lips; much smaller cortical regions represent less sensitive parts of the body.

Different parts of the body vary in their sensitivity to tactile and painful stimuli. These varying responses are based largely on the number and distribution of receptors. For example, the cornea is several hundred times more sensitive to painful stimuli than are the soles of the feet. The fingertips are good at touch discrimination, but the torso is not.

Neurologists measure sensitivity by determining the patient's two-point threshold, the distance between two points on the skin necessary in order for the individual to distinguish two distinct stimuli from just one. This method involves touching the skin with calipers at two points. Not surprisingly, acuity is greatest in the most densely nerve-packed areas of the body. The threshold is lowest on the fingers and lips.

The sensory fibers that respond to stimuli that damage tissue and can cause pain are called *nociceptors*. Different nociceptor subsets produce molecules that are responsible for the response to noxious (i.e., painful) thermal, mechanical, or chemical stimulation. Interestingly, these same molecules respond to plant-derived chemicals, such as capsaicin, garlic, and wasabi, that can produce pain. Some nociceptors in the skin respond to chemical stimuli that cause itch. Histamine is an example of such a nociceptor, and it can be released in response to certain bug bites or allergies.

Tissue injury also causes the release of numerous chemicals at the site of damage and inflammation. Prostaglandins enhance the sensitivity of receptors to tissue damage and ultimately can induce more intense pain sensations. Prostaglandins also contribute to the clinical condition of allodynia, in which innocuous stimuli can produce pain, as when sunburned skin is touched.

Persistent injury can lead to changes in the nervous system that amplify and prolong the "pain" signal. The result is a state of hypersensitivity in which pain persists and can even be evoked by normally innocuous stimuli. Persistent pain is in many respects a disease of the nervous system, not merely a symptom of some other disease process.

Sending and Receiving Pain and Itch Messages

Pain and itch messages are transmitted to the spinal cord via small, myelinated fibers and C fibers, very small, unmyelinated fibers. The myelinated nerve fibers are very pain-sensitive, and they probably evoke the sharp, fast pain that is produced by, for example, a pinprick. C fiber-induced pain, by contrast, is generally slower in onset, dull, and more diffuse.

In the ascending system, impulses are relayed from the spinal cord to several brain structures, including the thalamus and cerebral cortex. These structures are involved in the process by which pain or itch messages become a conscious experience. The experience of pain or itch is not just a function of the magnitude of the injury or even the intensity of the impulse activity generated. Other factors, such as the setting in which the injury occurs (e.g., in childbirth or in a car accident), as well as the emotional impact, also determine our overall response to the experience.

Pain messages can be suppressed by systems of neurons that originate within the gray matter in the brainstem. These descending systems suppress the transmission of pain signals from the dorsal horn of the spinal cord to higher brain centers. Some of these descending systems use naturally occurring chemicals, the endogenous opioids, or endorphins, which are functionally similar to morphine. Recent findings indicating that endorphins act at multiple opioid receptors in the brain and spinal cord have had important implications for pain therapy. For example, scientists began studying how to deliver opioids into the spine after discovering a dense distribution of opioid receptors in the spinal cord horn. After a technique for delivering opioids into the spine was used successfully in animals, such treatments were begun in humans; the technique is now common in treating pain after surgery.

Modern imaging tools are used to help scientists better understand what happens in the brain when pain is experienced. One finding is that no single area in the brain generates pain; rather, emotional and sensory components together constitute a mosaic of activity leading to pain. Interestingly, when people are hypnotized so that a painful *stimulus* is not experienced as unpleasant, activity in only some areas of the brain is suppressed, showing that the stimulus is still experienced. It just doesn't hurt anymore. As such techniques for brain study improve, it should be possible to monitor the changes in the brain that occur in people with persistent pain more effectively and to better evaluate the different painkilling drugs being developed.

Processing information from the sensory systems is only one of many functions of the brain. Such information is often the first step in other brain activities, including learning and retaining knowledge. The next chapter discusses what we know about these key functions as well as where gaps in our understanding remain.

Chapter 4:
Learning, Memory, and Language

In this Chapter

- Learning and Memory
- Language

Learning and Memory

A major breakthrough in understanding how the brain accomplishes learning and memory began with the study of a person known by his initials, H.M. As a child, H.M. developed a severe, difficult-to-treat form of epilepsy. When traditional therapies didn't help, H.M. underwent an experimental surgical treatment — the removal of the medial regions of his temporal lobes. The surgery worked in that it greatly alleviated the seizures, but it left H.M. with severe amnesia. He could remember recent events for only a few minutes and was unable to form explicit memories of new experiences. For example, after talking with him for a while and then leaving the room, upon returning, it would be clear that H.M. had no recollection of the exchange.

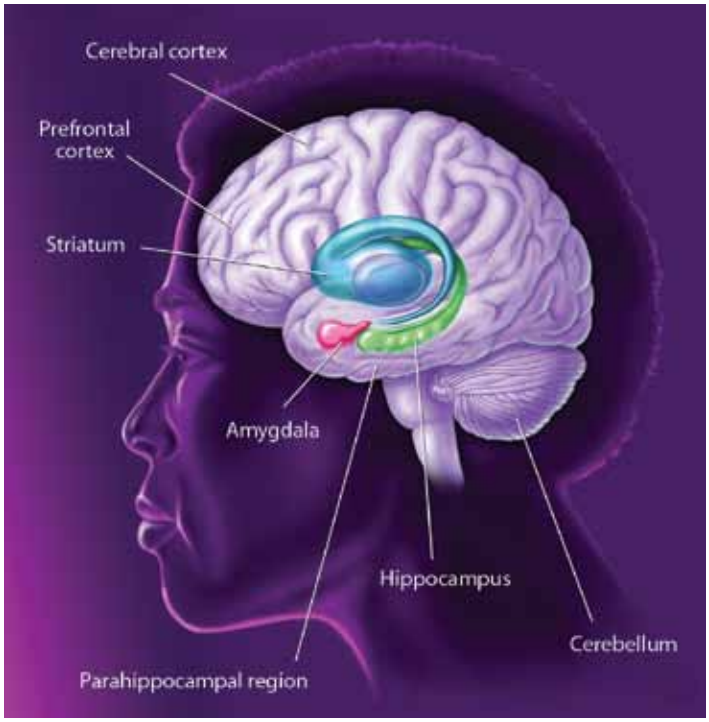
Despite his inability to remember new information, H.M. remembered his childhood very well. From these unexpected observations, researchers concluded that the parts of H.M.'s medial temporal lobe that were removed, including the hippocampus and parahippocampal region, played critical roles in converting short-term memories of experiences to long-term, permanent ones. Because H.M. retained some memories of events that occurred long before his surgery, it appeared that the medial temporal region was not the site of permanent storage but instead played a role in the organization and permanent storage of memories elsewhere in the brain.

Since that time, scientists have learned that the medial temporal region is closely connected to widespread areas of the cerebral cortex, including the regions responsible for thinking and language. Whereas the medial temporal region is important for forming, organizing, consolidating, and retrieving memory, it is the cortical areas that are important for long-term storage of detailed knowledge about facts and events and how this knowledge is used in everyday situations.

Different Facets of Memory

Our ability to learn and consciously remember everyday facts and events is called *declarative memory*. Studies using functional brain imaging have identified a large network of areas in the cerebral cortex that work together with the hippocampus to support declarative memory. These cortical areas play a distinct role in complex aspects of perception, movement, emotion, and cognition, each of which contributes to the overall experiences captured in declarative memories.

When we have new experiences, information initially enters working memory, a transient form of declarative memory. Working memory depends on the prefrontal



Different areas and systems of the brain are responsible for different kinds of memory. The hippocampus, parahippocampal region, and areas of the cerebral cortex (including the prefrontal cortex) work together to support declarative, or cognitive, memory. Different forms of nondeclarative, or behavioral, memory are supported by the amygdala, striatum, and cerebellum.

cortex as well as other cerebral cortical areas. Studies on animals have shown that neurons in the prefrontal cortex maintain relevant information during working memory and can combine different kinds of sensory information when required. In humans, the prefrontal cortex is highly activated when people maintain and manipulate memories.

Distinct areas within the prefrontal cortex support executive functions, such as selection, rehearsal, and monitoring of information being retrieved from long-term memory. To serve these functions, the prefrontal cortex also interacts with a large network of posterior cortical areas that encode, maintain, and retrieve specific types of information — visual images, sounds, and words, for example — as well as where important events occurred and much more.

Memory involves a persistent change in synapses, the connections between neurons.

Semantic memory is a form of declarative knowledge that includes general facts and data. Although scientists are just beginning to understand the nature and organization of cortical areas involved in semantic memory, it appears that different cortical networks are specialized for processing particular kinds of information, such as faces, houses, tools, actions, language, and many other categories of knowledge. Studies using functional imaging of normal humans have revealed zones within a large cortical expanse that selectively process different categories of information, such as animals, faces, or words.

Our memories of specific personal experiences that occurred at a particular place and time are called episodic memories. The medial temporal lobe areas are generally believed to serve a critical role in the initial processing and storage of these memories. Studies have shown that different parts of the parahippocampal region play distinct roles in processing "what," "where," and "when" information about specific events. The hippocampus links these elements of an episodic memory. The linkages are then integrated back into the various cortical areas responsible for each type of information.

The fact that H.M. and other people with amnesia show deficits in some types of memories and not others indicates that the brain has multiple memory systems supported by distinct brain regions. Nondeclarative knowledge, the knowledge of how to do something, often called procedural memory, is expressed in skilled behavior and learned habits and requires processing by the basal ganglia and cerebellum. The cerebellum is specifically involved in motor tasks that involve coordinated timing. The amygdala appears to play an important role in the emotional aspects of memory, attaching emotional significance to otherwise neutral stimuli and events. The expression of emotional memories also involves the hypothalamus and the sympathetic nervous system, both of which support emotional reactions and feelings. Thus, the brain appears to process different types of memories in separate ways.

Storing Memories

How exactly are memories stored in brain cells? After years of study, much evidence supports the idea that memory involves a persistent change in synapses, the connections between neurons. In animal studies, researchers found that such changes occur in the short term through biochemical events that affect the strength of the relevant synapses. Turning on certain genes may lead to modifications within neurons that change the strength and number of synapses, stabilizing new memories. Researchers studying the sea slug *Aplysia californica*, for example, can correlate specific chemical and structural changes in relevant cells with several simple forms of memory in the animal.

Another important model for the study of memory is the phenomenon of long-term potentiation (LTP), a long-lasting increase in the strength of a synaptic response following stimulation. LTP occurs prominently in the hippocampus, as well as in the cerebral cortex and other brain areas involved in various forms of memory. LTP takes place as a result of changes in the strength of synapses at contacts involving N-methyl-d-aspartate (NMDA) receptors.

Subsequently, a series of molecular reactions plays a vital role in stabilizing the changes in synaptic function that occur in LTP. These molecular events begin with the release of calcium ions into the synapse, activating the

Researchers identified cellular mechanisms of memory by studying the sea slug *Aplysia californica*. [Credit: Thomas J. Carew, PhD, New York University]

cyclic adenosine monophosphate (cAMP) molecule in the postsynaptic neuron. This molecule then activates several kinds of enzymes, some of which increase the number of synaptic receptors, making the synapse more sensitive to neurotransmitters. In addition, cAMP activates another molecule, called cAMP-response element binding protein (CREB). CREB operates within the nucleus of the neuron to activate a series of genes, many of which direct protein synthesis. Among the proteins produced are neurotrophins, which result in growth of the synapse and an increase in the neuron's responsiveness to stimulation.

Many studies have shown that the molecular cascade leading to protein synthesis is not essential to initial learning or to maintaining short-term memory; however, this cascade is essential for *long-term memory*. In addition, studies using genetically modified mice have shown that alterations in specific genes for NMDA receptors or CREB can dramatically affect the capacity for LTP in particular brain areas. What's more, the same studies have shown that these molecules are critical to memory.

The many kinds of studies of human and animal memory have led scientists to conclude that no single brain center stores memory. Instead, memory is most likely stored in distributed collections of cortical processing systems that are also involved in the perception, processing, and analysis of the material being learned. In short, each part of the brain most likely contributes differently to permanent memory storage.

Language

One of the most prominent human abilities is language, a complex system involving many components, including sensory-motor functions and memory systems. Although language is not fully understood, scientists have learned a great deal about this brain function from studies of patients who have lost speech and language abilities as a result of a stroke. Genetic analyses of developmental disorders of speech and language, as well as brain imaging studies of normal people, also have added to our knowledge.

It has long been known that damage to different regions within the left hemisphere produces different kinds of language disorders, or *aphasias*. Damage to the left frontal lobe can produce nonfluent aphasias, such as Broca's aphasia, a syndrome in which speech production abilities are impaired. Speech output is slow and halting, requires effort, and often lacks complexity in word or sentence structure. Although speaking is impaired, nonfluent aphasics still comprehend heard speech, although structurally complex sentences may be poorly understood.

Damage to the left temporal lobe can produce fluent aphasia, such as Wernicke's aphasia, in which comprehension of heard speech is impaired. Speech output, although of normal fluency and speed, is often riddled with errors in sound and word selection and tends to be unintelligible gibberish.

Damage to the superior temporal lobes in both hemispheres can produce word deafness, a profound inability to comprehend auditory speech on any level. Whereas Wernicke's aphasics can often comprehend bits and pieces of a spoken utterance, as well as isolated words, patients with word deafness are functionally deaf for speech, lacking the ability to comprehend even single words, despite being able to hear sound and even identify the emotional quality of speech or the gender of the speaker.

Research on aphasia has led to several conclusions regarding the neural basis of language. Researchers once believed that all aspects of language ability were governed only by the left hemisphere. Recognition of speech sounds and words, however, involves both left

and right temporal lobes. In contrast, speech production is a strongly left-dominant function that relies on frontal lobe areas but also involves posterior brain regions in the left temporal lobe. These appear to be important for accessing appropriate words and speech sounds.

Although the understanding of how language is both produced and understood by the brain is far from complete, several techniques, including genetic studies and imaging methods, have increasingly been put to use. Through the use of these tools, we can expect to gain important insights into this critical aspect of brain function.

Scientists have learned a great deal about language by studying patients who have lost speech and language abilities.

During the last decade, novel insights have emerged through molecular genetic studies of inherited disorders that impede the development of fluent speech and language. For example, rare mutations of a gene called *FOXP2* impede learning to make sequences of mouth and jaw movements that are involved in speech, accompanied by difficulties that affect both spoken and written language. The *FOXP2* gene codes for a special type of protein that switches other genes on and off in particular parts of the brain. Changes in the sequence of this gene may have been important in human evolution. Researchers are studying the differences in this gene between humans and animals to learn more about the development of language.

Functional imaging methods, too, have identified new structures involved in language. Systems involved in accessing the meaning of words appear to be located (in part) in the middle and inferior portions of the temporal lobe. In addition, the anterior temporal lobe is under intense investigation as a site that may participate in some aspect of sentence-level comprehension.

Recent work has also identified a sensory-motor circuit for speech in the left posterior temporal lobe, which is thought to help the systems for speech recognition and speech production communicate with each other. This circuit is involved in speech development and is thought to support verbal short-term memory.

Equally important is the brain's role in movement. For example, part of language is using the muscles of the mouth and jaw correctly to produce sounds. Throughout the body, muscles allow us to move in many complex ways. The next chapter discusses the intricate interplay between the brain and muscles in our body.

Chapter 5: Movement

In this Chapter

- Involuntary Movements
- More Complex Movements

From the stands at sports events, we marvel at the perfectly placed serves of professional tennis players and the lightning-fast double plays executed by big league baseball infielders. But in fact, each of us in our daily activities performs a host of complex, skilled movements — such as walking upright, speaking, and writing — that are just as remarkable. What's more, movement also reflects our mood and state of mind. For example, posture and patterns of movement can indicate whether we are happy or sad. Facial expressions such as a smile and a frown have a universal meaning.

These and all of our actions are made possible by a finely tuned and highly complex central nervous system, which controls the actions of hundreds of muscles. Through new experiences — and the formation of new neural connections — the nervous system can adapt to changing movement requirements to accomplish these everyday marvels. With practice, these movements can be performed even more skillfully.

To understand how the nervous system performs such feats, we have to start with the muscles, the body parts that produce movement under the control of the brain and spinal cord. Most muscles attach to points on the skeleton and cross one or more joints. The close relationship of these muscles to the skeleton gives them their name — skeletal muscles. Activation of a given muscle can open or close the joints that it spans, depending on whether it is a joint flexor (closer) or an extensor (opener). Flexors and extensors work in opposition to each other, causing the contraction of some muscles and the lengthening of others. For example, bending the elbow involves contraction of the biceps and lengthening of the triceps. Muscles that move a joint in an intended direction are called *agonists*, and those that oppose this direction of movement are *antagonists*. Skilled movements at high speed are started by agonists and stopped by antagonists, thus ensuring that the joint or limb is returned to the desired position.

Each skeletal muscle is made up of thousands of individual muscle fibers, and each muscle fiber is controlled by one alpha motor neuron in either the brain or the spinal cord. Furthermore, each single alpha motor neuron controls many muscle fibers (ranging from a few to 100 or more); an alpha motor neuron and all the muscle fibers it contains form a functional unit referred to as a *motor unit*. Motor units are the critical link between the brain and muscles. If the motor neurons die, which can happen in certain diseases, such as amyotrophic lateral sclerosis (ALS), a person is no longer able to move.

Some muscles act on soft tissue, such as the muscles that move the eyes and tongue and those that control facial expressions. These muscles also are under control of the central nervous system. They operate in much the same way as those that attach to bone.

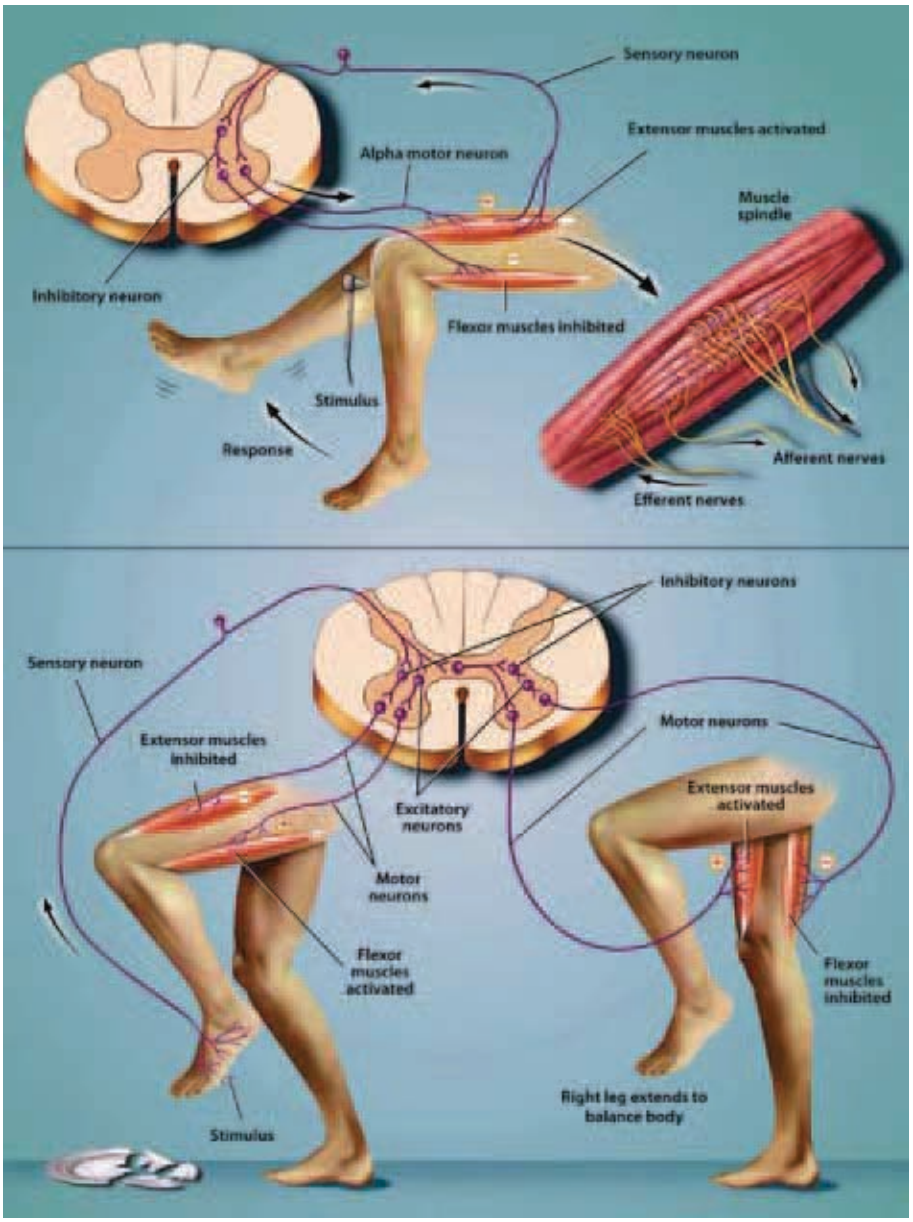
Involuntary Movements

Perhaps the simplest and most fundamental movements are *reflexes*. These are relatively fixed, automatic muscle responses to particular stimuli, such as the slight extension of the leg when a physician taps the knee with a small rubber hammer. All reflexes involve the activation of small sensory receptors in the skin, the joints, or even in the muscles themselves. For example, the reflexive knee movement is produced by a slight stretch of the knee extensor muscles when the physician taps the muscle tendon at the knee. This slight muscle stretch is "sensed" by receptors in the muscle called muscle spindles. Innervated by sensory fibers, the spindles send information to the spinal cord and brain about the length and speed of the shortening or lengthening of a muscle. This information is used to control both voluntary and involuntary movements. A sudden muscle stretch sends a barrage of impulses into the spinal cord along the muscle spindle sensory fibers. In turn, these fibers activate motor neurons in the stretched muscle, causing a contraction called the stretch reflex. The same sensory stimulus causes inactivation, or inhibition, of the motor neurons of the antagonist muscles through connecting neurons, called inhibitory interneurons,

within the spinal cord. Thus, even the simplest of reflexes involves a coordination of activity across motor neurons that control agonist and antagonist muscles.

The brain can control not only the actions of motor neurons and muscles but even the nature of the feedback received as movements occur. For example, the sensitivity of the muscle spindle organs is monitored by the brain through a separate set of gamma motor neurons that control the specialized muscle fibers and allow the brain to fine-tune the system for different movement tasks. Other specialized sense organs in muscle tendons — the Golgi tendon organs — detect the force applied by a contracting muscle, allowing the brain to sense and control the muscular force exerted during movement. These complex feedback systems are coordinated and organized to respond differently for tasks that require precise control of position, such as holding a full teacup, than they do for those requiring rapid, strong movement, such as throwing a ball.

Another useful reflex is the flexion withdrawal that occurs when the bare foot encounters a sharp object. The leg is immediately lifted from the source of potential injury (flexion), but the opposite leg responds with increased extension so that we can maintain our balance. The latter event is called the crossed extension



The stretch reflex (top) occurs when a doctor taps a muscle tendon to test your reflexes. This sends a barrage of impulses into the spinal cord along muscle spindle sensory fibers, activating motor neurons to the stretched muscle. This series of events cause a contraction, completing the stretch reflex. Flexion withdrawal (bottom) occurs when your bare foot encounters a sharp object. Your leg is immediately lifted (flexion) from the source of potential injury, but the opposite leg responds with increased extension so that you can maintain your balance. The latter event is called the crossed extension reflex.

reflex. These responses occur very rapidly and without your attention because they are built into systems of neurons that are located within the spinal cord itself.

More Complex Movements

Networks of spinal neurons also participate in controlling the alternating action of the legs during normal walking, maintaining posture, and, to a large degree, in all movements. In fact, the basic patterns of muscle activation that produce coordinated walking can be generated not only in four-footed animals, but also in humans, within the spinal cord itself. These spinal mechanisms, which evolved in primitive vertebrates, are being studied to determine the degree to which spinal circuitry can be used to recover basic postural and locomotor function after severe paralysis.

The most complex movements that we perform, including voluntary ones that require conscious planning, involve control of these basic spinal mechanisms by the brain. Scientists are only beginning to understand the complex interactions that take place among different brain regions during voluntary movements, mostly through careful experiments on animals.

One important brain area that is responsible for voluntary movement is the motor cortex, which exerts powerful control over the spinal cord, in part through direct control of its alpha motor neurons. Some neurons in the motor cortex appear to specify the coordinated action of many muscles to produce the organized movement of a limb to a particular point in space. Others appear to control only two or three functionally related muscles, such as those of the hand or arm, that are important for finely tuned, skilled movement.

In addition to the motor cortex, movement control involves the interaction of many other brain regions, including the basal ganglia, thalamus, cerebellum, and a large number of neuron groups located within the midbrain and brainstem — regions that send axons to the spinal cord. Scientists know that the basal ganglia and thalamus have widespread connections with motor and sensory areas of the cerebral cortex.

Dysfunction of the basal ganglia can lead to serious movement disorders. The neurotransmitter dopamine, which helps control movement, is supplied to the basal ganglia by the axons of neurons located in the substantia nigra, a midbrain cell group. People with Parkinson's disease experience degeneration of the nigral neurons. The supply of dopamine is depleted, resulting in the hallmark symptoms of Parkinson's — tremor, rigidity, and akinesia, the inability to move.

Another brain region that is crucial for coordinating and adjusting skilled movement is the cerebellum. A disturbance of cerebellar function leads to poor coordination of muscle control, disorders of balance and reaching, and even difficulties in speech, one of the most intricate forms of movement control.

The cerebellum helps us adjust motor output to deal with changing conditions.

The cerebellum receives direct information from all the sensory receptors in the head and the limbs and from most areas of the cerebral cortex. The cerebellum apparently acts to integrate all this information to ensure smooth coordination of muscle action, enabling us to perform skilled movements more or less automatically. Considerable evidence indicates that the cerebellum helps us adjust motor output to deal with changing conditions, such as growth, disability, changes in weight, and aging. It tunes motor output to be appropriate to the specific requirements of each new task: Our ability to adjust when picking up a cup of coffee that is empty or full depends on the cerebellum. Evidence suggests that as we learn to walk, speak, or play a musical instrument, the necessary, detailed control information is stored within the cerebellum, where it can be called upon by commands from the cerebral cortex.

Just as the brain controls movement, it also is responsible for one of the body's most important functions — sleep. As explained in Chapter 6, the brain switches back and forth between different stages of sleep all night long.