# BrainFacts

## A PRIMER ON THE BRAIN AND NERVOUS SYSTEM

**A companion to BrainFacts.org**

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# 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.

# Contents

# 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 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*.

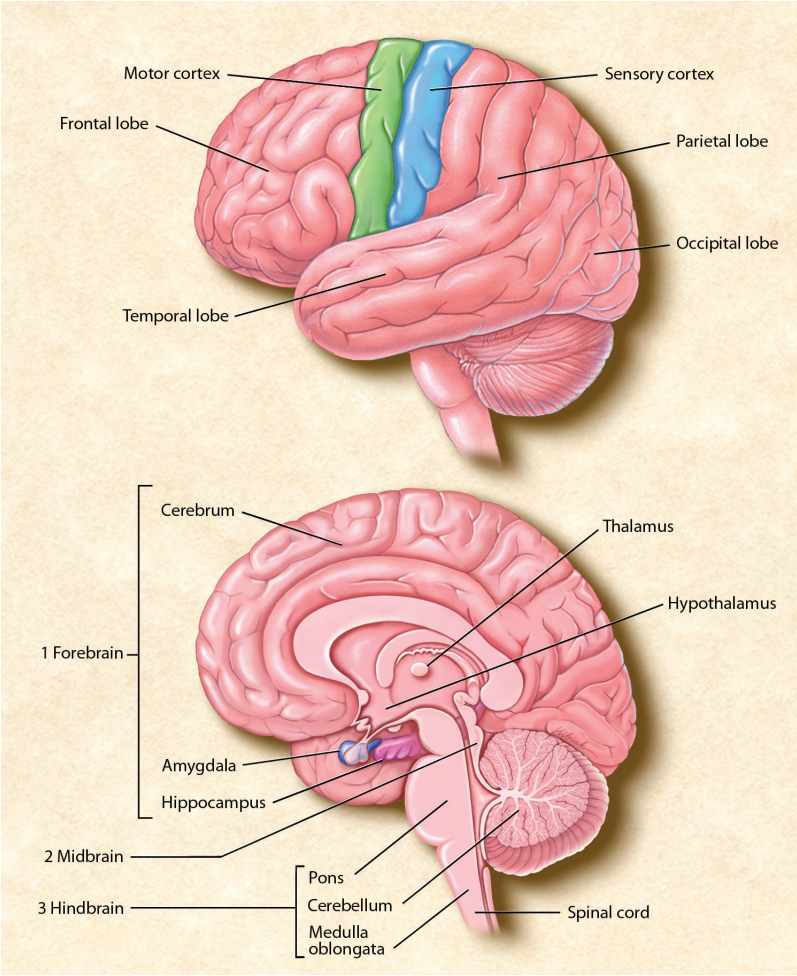
All of these structures make up the forebrain. Other key parts of the *forebrain* include the *basal ganglia*, which are cerebral nuclei deep in the cerebral cortex; the *thalamus*; and the *hypothalamus*. The cerebral nuclei help coordinate muscle movements and reward useful behaviors; the thalamus 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.

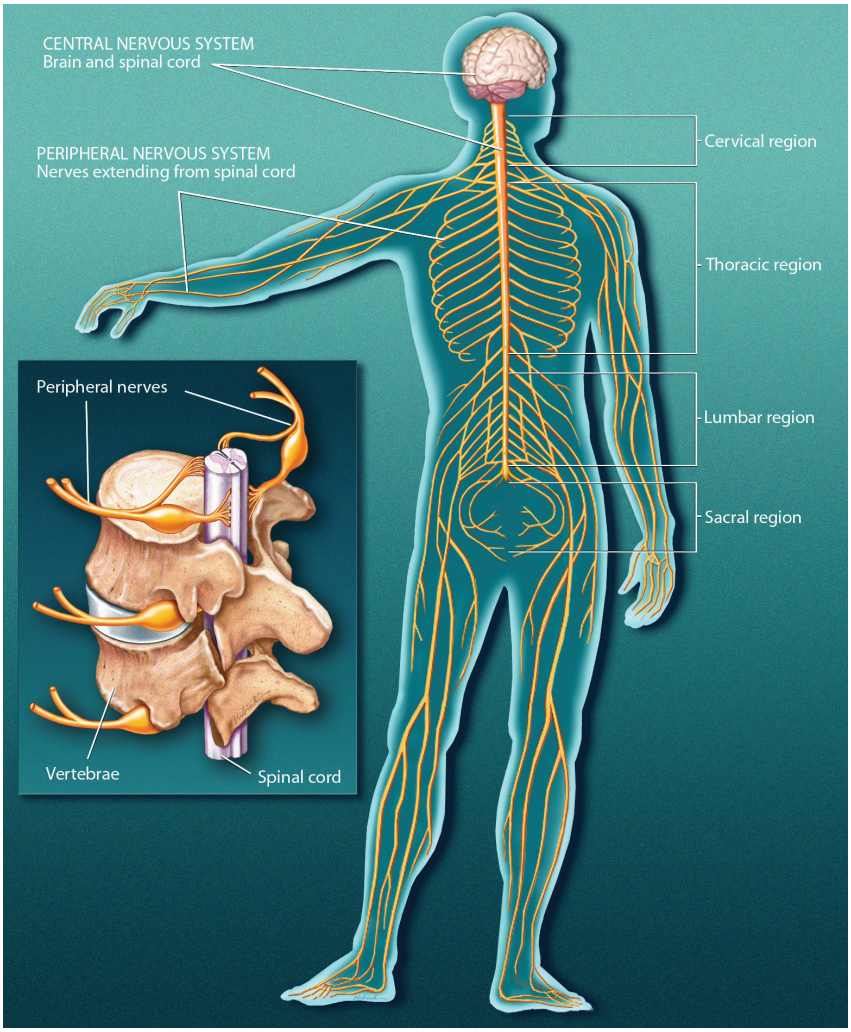
The *autonomic nervous system* is made of neurons connecting the CNS with internal organs. It is divided into two parts. The *sympathetic nervous system* mobilizes energy and resources during times of *stress* and arousal, while the *parasympathetic nervous system* conserves energy and resources during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

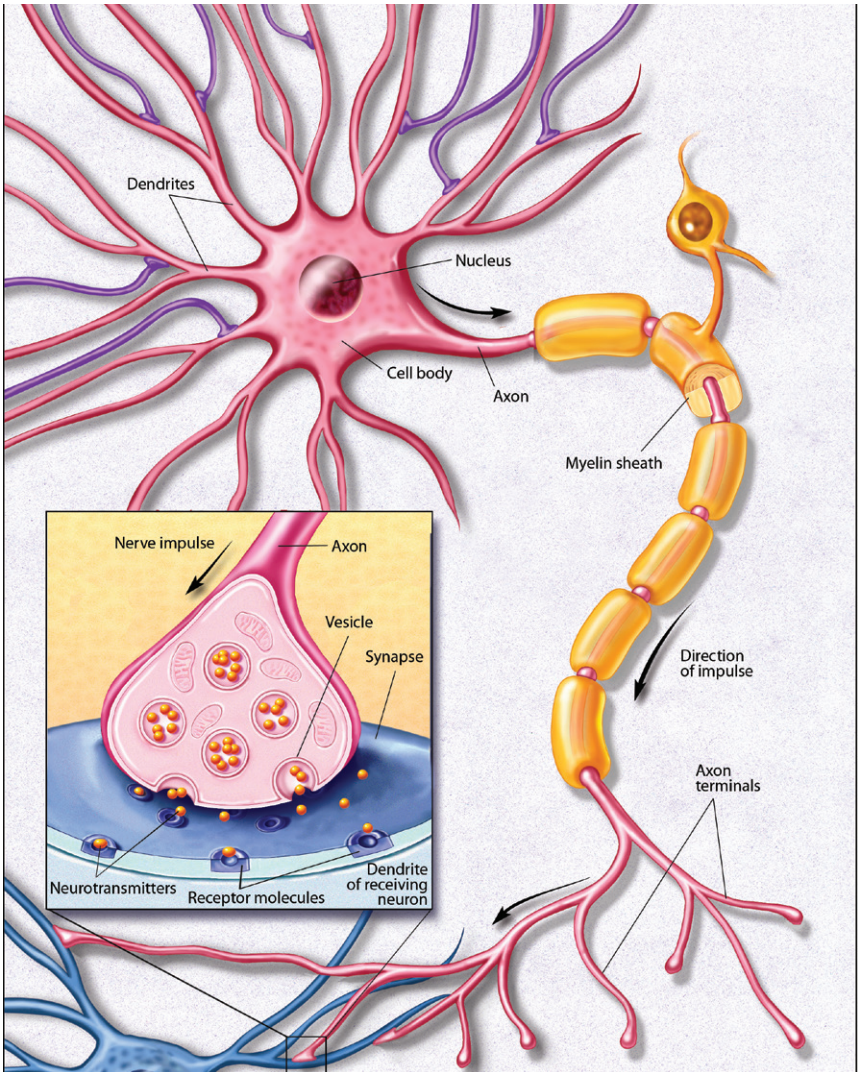
There are many different kinds of neurotransmitters, and they all play an essential role in the human body. The next section provides a summary of key neurotransmitters and neuromodulators, chemicals that help shape overall activity in the brain.

## 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 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.

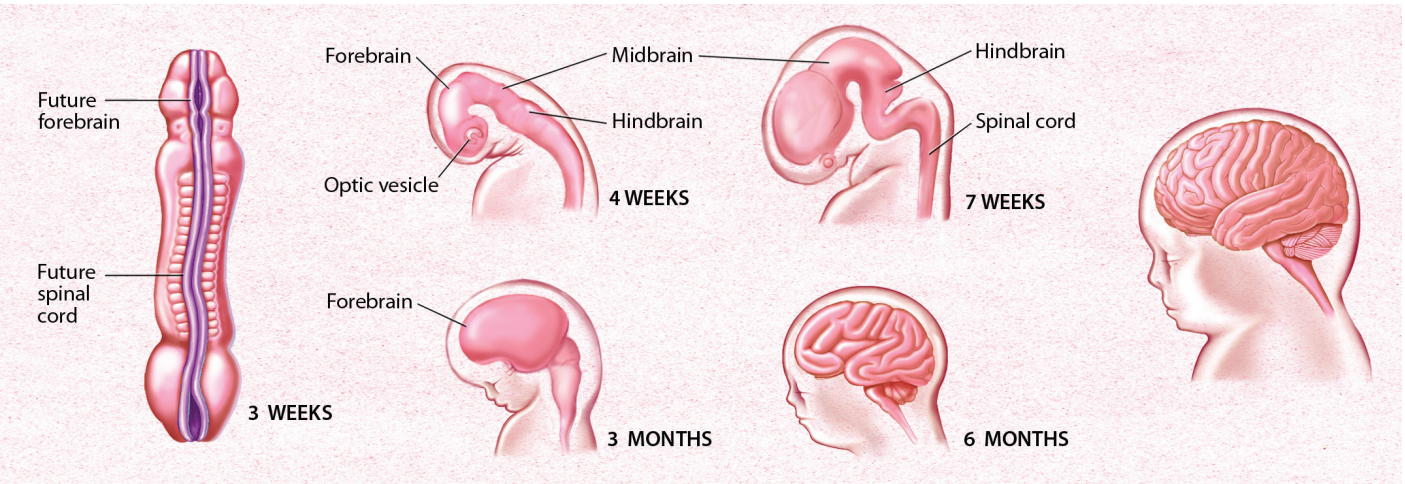
## The Journey of Nerve Cells

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.

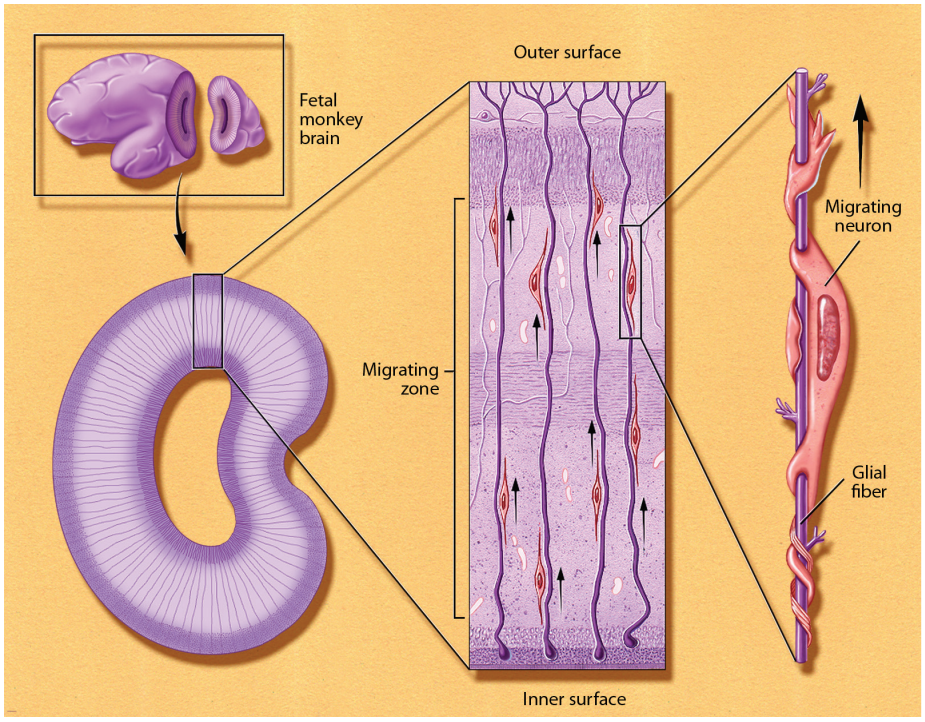
*Growth cones*, enlargements on the axon's tip, actively explore the environment as they seek out their precise destination. Researchers have discovered many special molecules that help guide growth cones. Some molecules lie on the cells that growth cones contact, whereas others are released from sources 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.

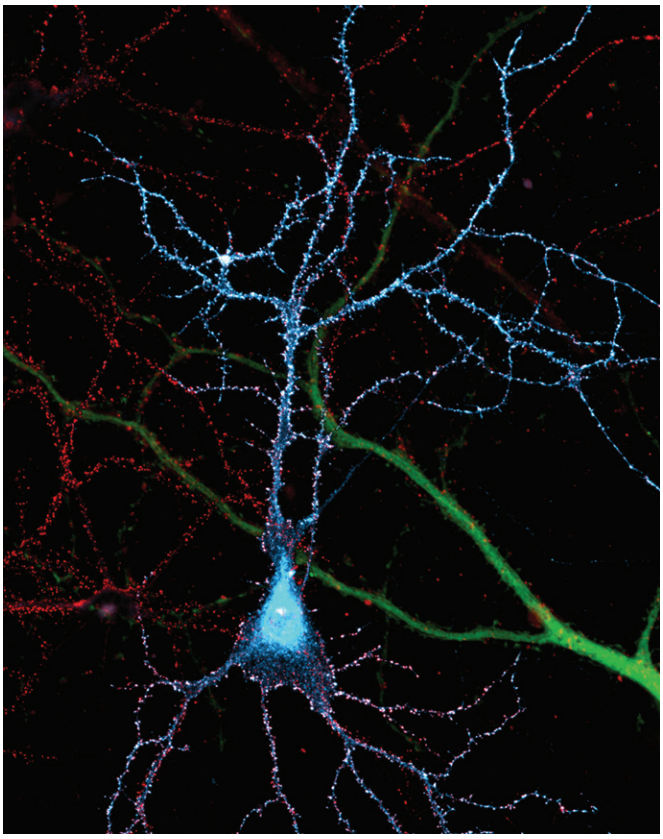
Researchers have successfully identified ways in which the synapse differentiates once contact has been made. The tiny portion of the axon that contacts the dendrite becomes specialized for the release of neurotransmitters, and the tiny portion of the dendrite that receives the contact becomes specialized 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.

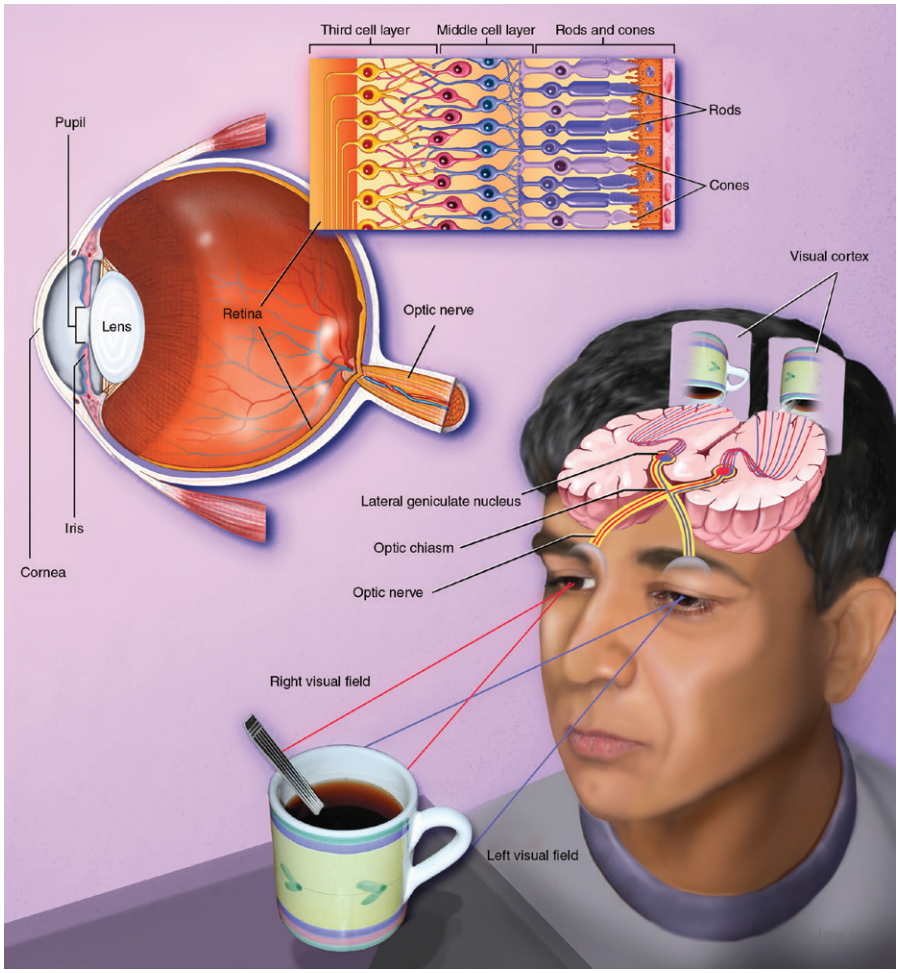
Primates, including humans, have well-developed vision using two eyes, called binocular vision. Visual signals pass from each eye along the million or so fibers of the optic nerve to the optic chiasm, where some nerve fibers cross over. This crossover allows both sides of the brain to receive signals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

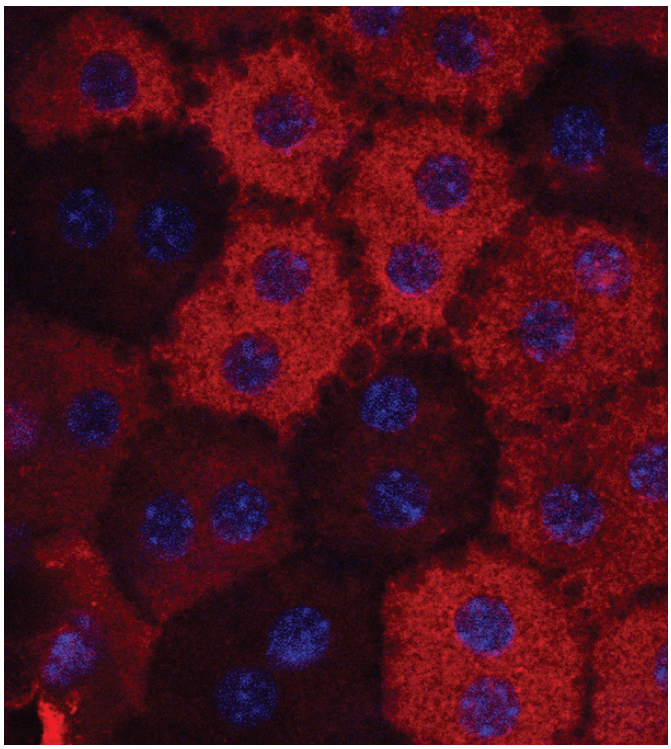
signals are fed into at least three separate processing systems. One system appears to process information mainly about shape; a second, mainly about color; and a third, movement, location, and spatial organization. Human psychological studies support the findings obtained through animal research. These 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.



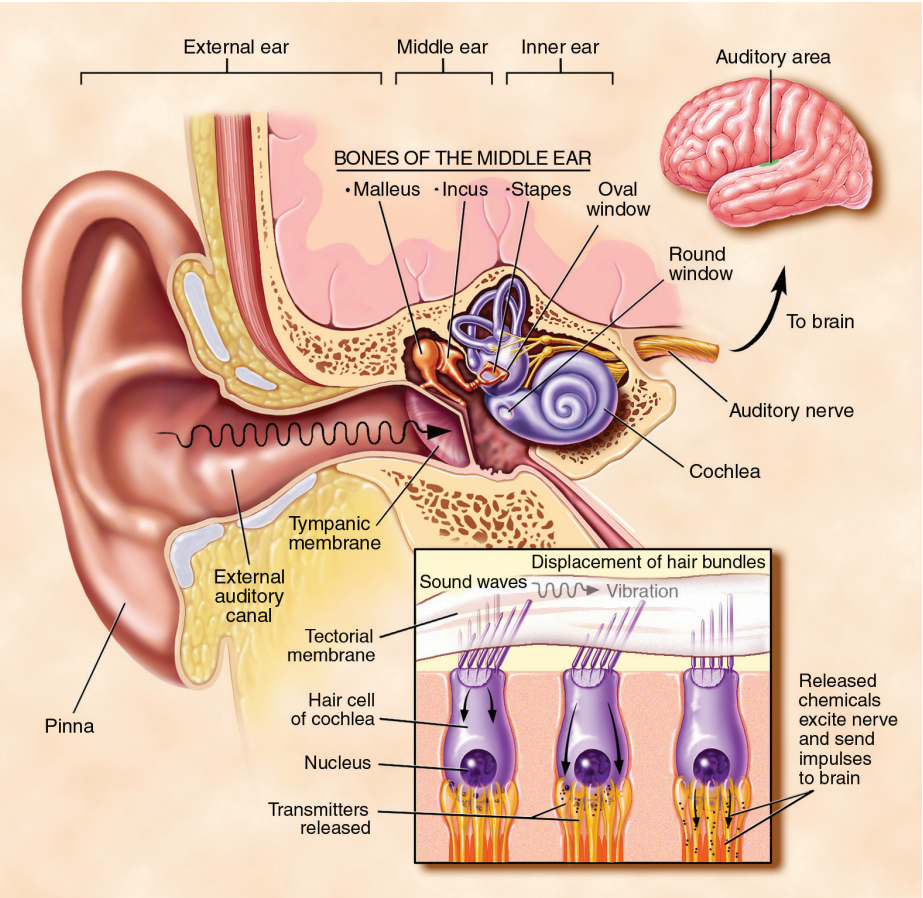
Mutations in the RPE65 protein (labeled in retinal cells in red) cause an inherited form of blindness that may be corrected by gene therapy. [Credit: National Eye Institute, National Institutes of Health]

## 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

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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.

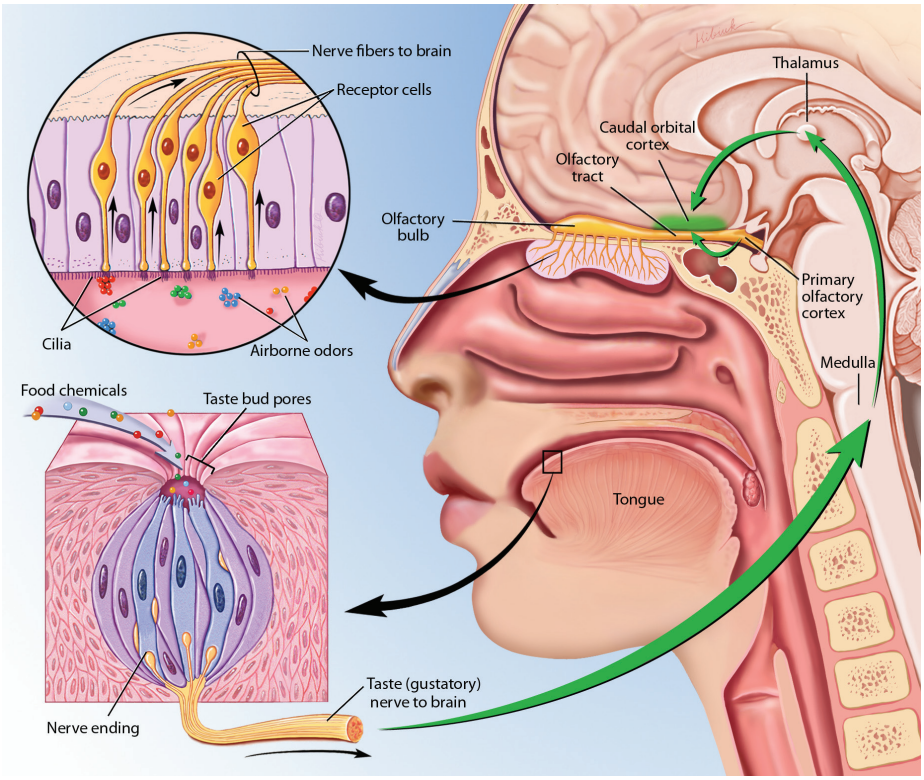
In the auditory cortex, adjacent neurons tend to respond to tones of similar frequency. However, they specialize in different combinations of tones. Some respond to pure tones, such as those produced by a flute, and some to complex sounds like those made by a violin. Some respond to long sounds and some 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.

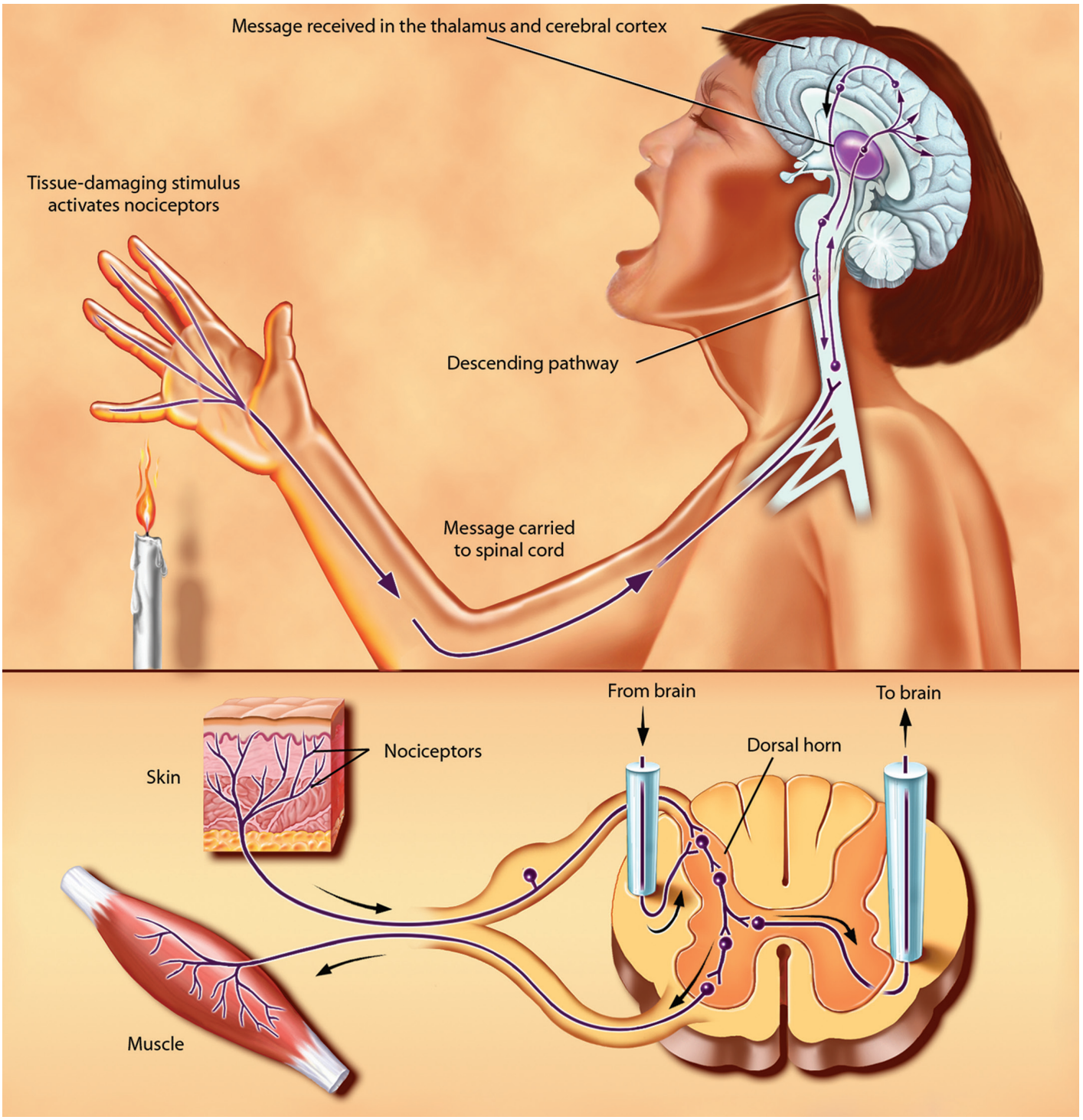
Airborne odor molecules, called odorants, are detected by specialized sensory neurons located in a small patch of mucus membrane lining the roof of the nose. Axons of these sensory cells pass through perforations in the overlying bone and enter two elongated *olfactory bulbs* lying against the underside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

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.

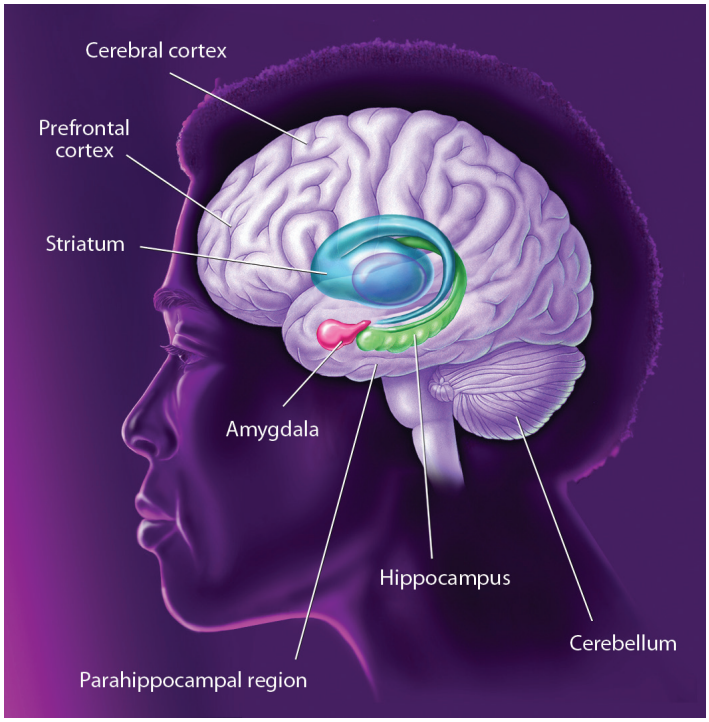
Despite his inability to remember new information, H.M. remembered his childhood very well. From these unexpected observations, researchers concluded that the parts of H.M.'s medial temporal lobe that were removed, including the hippocampus and parahippocampal region, played critical roles in converting 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.

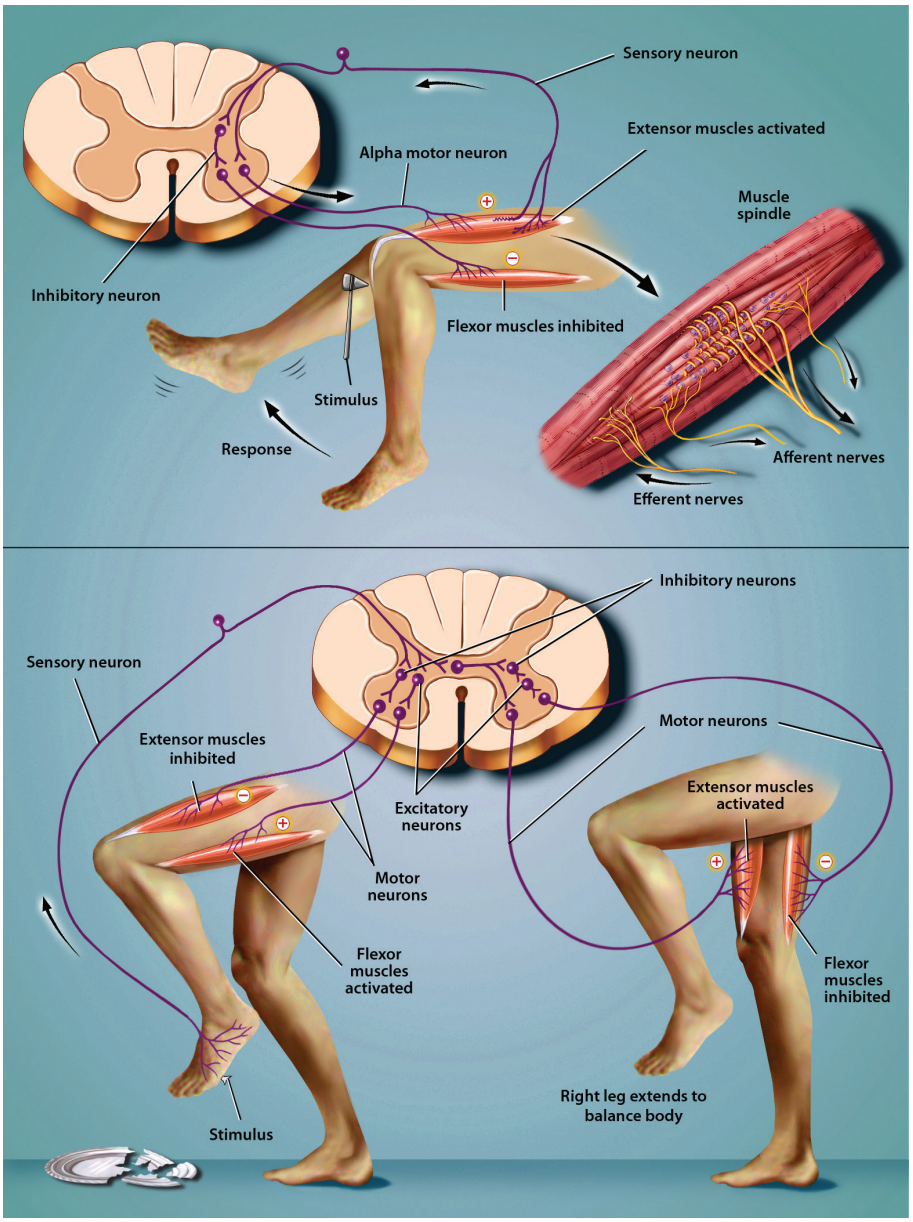
## Involuntary Movements

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.

# Chapter 6: Sleep

## In this Chapter



We spend nearly one-third of our lives asleep. Sleep is crucial for concentration, memory, coordination, and even emotional health. Without enough sleep, people have trouble focusing and responding quickly when they need to, such as when they're behind the wheel of a car. In fact, sleep loss can have as great an effect on performance as drinking alcohol. And growing evidence suggests that a lack of sleep increases the risk of a variety of health problems, including diabetes, cardiovascular disease and heart attacks, stroke, *depression*, high blood pressure, obesity, and infections.

Although much research has been done on sleep, it remains one of the great mysteries of modern neuroscience. Over the past few years, however, researchers have made tremendous headway in understanding some of the brain circuitry that controls wake-sleep states.

Scientists now recognize that sleep consists of several different stages. What's more, the choreography of a night's sleep involves the interplay of these stages, a process that depends on a complex switching mechanism between sleep-wake states. Sleep stages are accompanied by daily rhythms in hormones, body temperature, and other functions.

There are pressing reasons why understanding the mechanisms behind sleep is so important. Sleep disorders are among the nation's most common health problems, affecting up to 70 million people, most of whom are undiagnosed and untreated. These disorders are one of the least recognized sources of disease, disability, and even death, costing an estimated $15.9 billion annually. Research holds promise for devising new treatments to allow millions of people to get a good night's sleep.

## Brain Activity During Sleep

Although sleep appears to be a passive and restful time, it actually involves a highly active and well-scripted interplay of brain circuits, resulting in sleep's various stages. These stages were discovered in the 1950s through experiments using *electroencephalography* (EEG) to examine human brain waves. Researchers also measured movements of the eyes and the limbs.

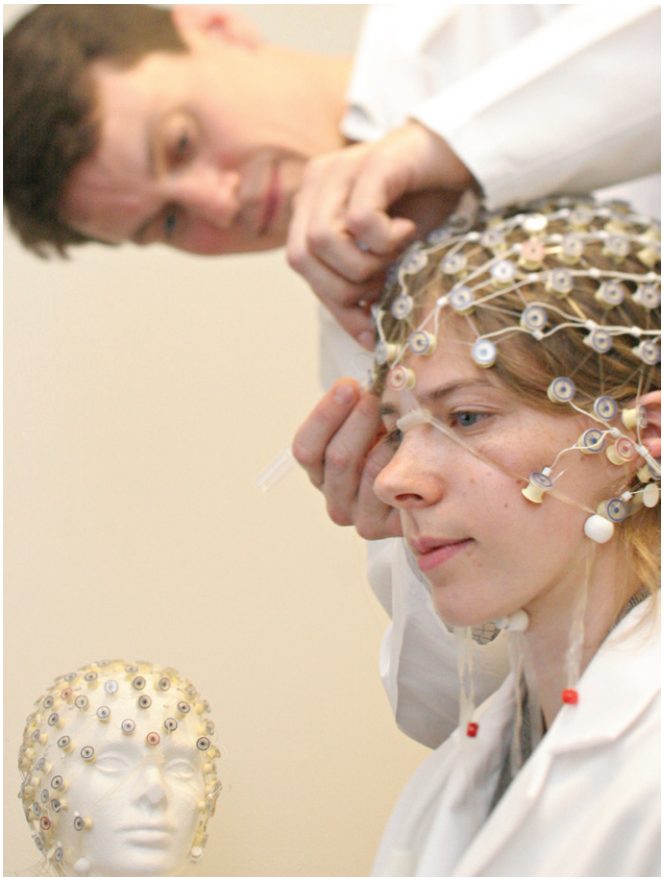
The results of these experiments were telling. Researchers found that each night, over the course of the first hour or so of sleep, the brain progresses through a series of stages during which brain waves slow down. This period of slow wave sleep is accompanied by relaxation of the muscles and the eyes. Heart rate, blood pressure, and body temperature all fall. If awakened during this time, most people recall only fragmented thoughts, not active dreams.

Over the next half hour or so, brain activity alters drastically, from deep slow wave sleep to *rapid eye movement (REM)* sleep, characterized by neocortical EEG waves similar to those observed during waking. Paradoxically, the fast, waking-like EEG activity is accompanied by *atonia*, or paralysis of the body's muscles. Only the muscles that allow breathing and control eye movements remain active. During REM sleep, active dreaming takes place. Heart rate, blood pressure, and body temperature become much more variable. Men often have erections during this stage. The first REM period usually lasts 10 to 15 minutes.

During the night, these cycles of slow wave and REM sleep alternate, with the slow wave sleep becoming less deep and the REM periods more prolonged until waking occurs. Over the course of a lifetime, the pattern of sleep cycles changes. Infants sleep up to 18 hours per day, and they spend much more time in deep slow wave sleep. As children mature, they spend less time asleep and less time in deep slow wave sleep. Older adults may sleep only six to seven hours per night. What's more, adults often complain of early waking that they cannot avoid and spend very little time in slow wave sleep.

## Sleep Disorders

The most common sleep disorder, and the one most people are familiar with, is insomnia. Some insomniacs have difficulty falling asleep initially, but others fall asleep



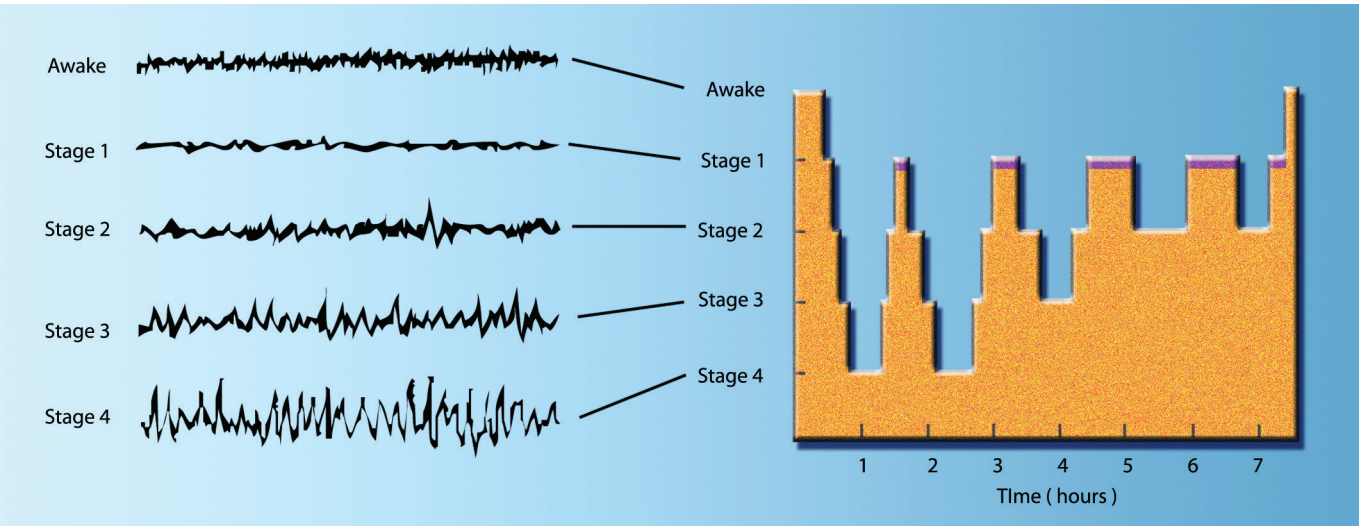
In EEG, electrodes placed around the head record electrical activity of the human brain in response to a variety of stimuli and activities — even sleep.

and then awaken partway through the night and cannot fall asleep again. Although a variety of short-acting sedatives and sedating antidepressant drugs are available to help, none produces a truly natural and restful sleep state because they tend to suppress the deeper stages of slow wave sleep. They also are not effective in helping people stay asleep.

Many of the most common disorders, listed below, disrupt sleep and result in inadequate amounts of sleep, particularly of the deeper stages.

- Excessive daytime sleepiness, which has many causes.
- Obstructive sleep apnea occurs as sleep deepens and the airway muscles in the throat relax to the point of collapse, closing the airway. The individual has difficulty breathing and wakes up without entering the deeper stages of slow wave sleep. This condition can cause high blood pressure and may increase the risk of heart attack. Increased daytime sleepiness that results from sleep apnea can lead to an increased risk of daytime accidents, especially automobile accidents. Treatment may include a variety of strategies to reduce airway collapse during sleep. Whereas simple things like losing weight, avoiding alcohol and sedating drugs prior to sleep, and avoiding sleeping on one's back can sometimes help, most people with sleep apnea require devices that induce continuous positive airway pressure to keep the airway open. One such device is a small mask that fits over the nose to provide an airstream under pressure during sleep. In some cases, surgery is needed to correct the airway anatomy.
- Periodic limb movements of sleep are intermittent jerks of the legs or arms that occur as the individual enters slow wave sleep. These movements can cause arousal from sleep. A related disorder, called REM behavior disorder, occurs when muscles fail to become paralyzed during REM sleep, As a result, people literally act out their dreams by getting up and moving around. Needless to say, this disorder can be very disruptive to a normal night's sleep. Both disorders are more common in people with Parkinson's disease, and both can be treated with drugs for Parkinson's or with a benzodiazepine called clonazepam.
- Narcolepsy is a relatively uncommon condition — only one case per 3,000 people — in which the switching mechanisms controlling the transitions into sleep, particularly REM sleep, do not work properly. This problem is due to the loss of nerve cells in the lateral hypothalamus that contain the neurotransmitter orexin (also known as hypocretin). People with narcolepsy have sleep attacks during the day, in which they suddenly fall asleep. This is socially disruptive, as well as dangerous; for example, if a sleep attack strikes while someone with narcolepsy is driving, it could result in an accident. People with narcolepsy tend to enter REM sleep very quickly as well and may even enter a dreaming state while still partially awake, a condition known as hypnagogic hallucination. They also have attacks during which they lose muscle tone — a state similar to what occurs during REM sleep but instead happens while they are awake. These attacks of paralysis, known as cataplexy, can be triggered by emotional experiences, even by hearing a funny joke.

Recently, studies into the mechanism of narcolepsy have given researchers important insights into the processes that




This chart shows the brain waves of a young adult recorded by an electroencephalogram (EEG) during a night's sleep. As the adult passes into deeper stages of sleep, the brain waves slow down and become larger. Throughout the night, the individual goes through these stages multiple times, with brief periods of REM sleep, during which the EEG is similar to wakefulness.

control these mysterious transitions between waking, slow wave sleep, and REM sleep states.

## How Is Sleep Regulated?

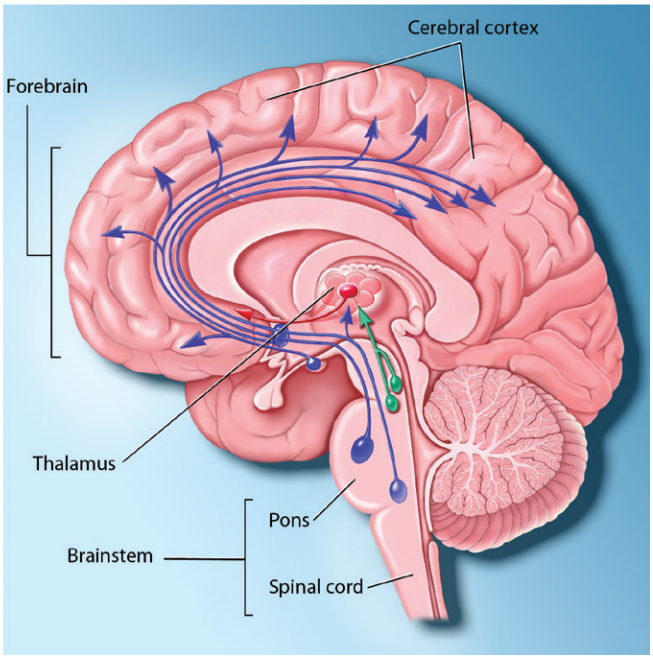
What is the difference between sleep and wakefulness? Much of it depends on which brain systems are activated. Wakefulness is maintained by several brain systems, each regulating different aspects of this state. Many of the systems are located in the upper brainstem, where nerve cells using the neurotransmitters acetylcholine, norepinephrine, serotonin, and glutamate connect with the forebrain. Nerve cells containing orexin, in the hypothalamus, are also important in wakefulness — and, as mentioned above, their loss causes narcolepsy. Hypothalamic nerve cells containing the neurotransmitter histamine play a key role as well. Activation of the thalamus and the basal forebrain by acetylcholine is particularly important in maintaining activity in the cerebral cortex and consciousness. This level of alertness is reflected in an activated, low-voltage EEG.

During non-REM sleep, these arousing systems become much less active, and the transmission of information from the senses through the thalamus is curtailed. Consciousness lessens, and wakefulness gives way to the slow wave pattern typical of the first stage of sleep. During this state, there is active suppression of arousal systems by a group of nerve cells in the hypothalamus, called the ventrolateral preoptic (VLPO) nucleus. The cells in the VLPO contain the inhibitory neurotransmitters galanin and GABA. Damage to the VLPO nucleus produces irreversible insomnia.

The state of REM sleep is characterized by an internally activated brain and an activated EEG — but with external input suppressed. Internal activation during REM comes from a cyclically active REM sleep generator made up of neurons in the brainstem. Signals from these neurons cause the forebrain to become excited and lead to the rapid eye movements and muscle suppression — hallmark signs of this state. In the absence of external input, forebrain excitation from internal sources is the driving force behind the vivid dreams experienced during REM sleep. Interestingly, our motor cortex nerve cells fire as rapidly during REM sleep as they do during waking movement, a fact that explains why movement can coincide with dreams. The periodic recurrence of REM sleep about every 90 minutes during sleep is thought to be caused by the on-off switching of REM-generating neurons, which produce acetylcholine and glutamate, and REM-suppressive neurons, which produce norepinephrine, serotonin, and GABA.

## The Sleep-Wakefulness Cycle

Why do we get sleepy? There are two main determining factors: the *circadian system* (time of day or night) and how long we have been awake. The circadian timing system is regulated by the *suprachiasmatic nucleus*, a small group of nerve cells in the hypothalamus that acts as a master clock. These cells express clock proteins, which go through a biochemical cycle




Wakefulness is maintained by activity in two systems of neurons, shown in green and red. The green pathway shows neurons that make the neurotransmitter acetylcholine in the brainstem, while the red pathway is in the forebrain. The brainstem arousal center supplies the acetylcholine for the thalamus and brainstem, and the forebrain center supplies the cerebral cortex. Activation in these centers alone can create rapid eye movement sleep. Activation of other neurons that make the neurotransmitters norepinephrine, serotonin, and histamine, shown in the blue pathways, is needed for waking.

of about 24 hours, setting the pace for daily cycles of activity, sleep, hormone release, and other bodily functions. Researchers first identified these proteins and determined their important roles in sleep by studying the fruit fly *Drosophila melanogaster*. The suprachiasmatic nucleus also receives input directly from the retina, and the clock can be reset by light so that it remains linked to the outside world's day-night cycle. In addition, the suprachiasmatic nucleus provides signals to an adjacent brain area, called the subparaventricular nucleus, which in turn contacts the dorsomedial nucleus of the hypothalamus. The dorsomedial nucleus then contacts the ventrolateral preoptic nucleus and the *orexin neurons* in the lateral hypothalamus. It is these neurons that directly regulate sleep and arousal.

Orexin provides an excitatory signal to the arousal system, particularly to the norepinephrine neurons. Indeed, recent work using selective stimulation of orexin neurons by artificially inserted receptors sensitive to fiberoptic light pulses — a process referred to as optogenetic stimulation — produces arousal. This arousal is mediated by orexin activation of norepinephrine neurons in the locus coeruleus. Orexin activation plays a critical role in preventing abnormal transitions into REM sleep during the day, as occurs in narcolepsy. In experiments with mice, in which the gene for the neurotransmitter orexin was experimentally removed, the animals became narcoleptic. In humans with narcolepsy, the orexin levels in the brain and spinal fluid are abnormally low.

The second system regulating sleepiness is the homeostatic system, which responds to progressively longer wake periods by increasing the urge to sleep. The subjective sense of the increasing need to sleep coinciding with increasing wakefulness suggests that there might be a brain physiological parallel; that is, the longer a person is awake, the greater the likelihood of an increase in sleep-inducing factor(s). Evidence now suggests that one important sleep factor is the inhibitory neurochemical *adenosine*. With prolonged wakefulness, increasing levels of adenosine are evident in the brain, initially in the basal forebrain and then throughout the cortex. The increased levels of adenosine serve the purpose of slowing down cellular activity and diminishing arousal. Adenosine levels then decrease during sleep.

These studies of adenosine prompted examination of the compound adenosine triphosphate (ATP), the cellular energy source that powers nerve cells in the brain. Brain adenosine may be produced by ATP breakdown in the course of the high brain activity that takes place during wakefulness. Since nerve cell activity decreases and adenosine levels decline in non-REM sleep, the logical assumption is that ATP increases during sleep. Indeed, studies in animals found that brain ATP levels soared during the initial hours of non-REM sleep. Because ATP is needed to produce adenosine, which is essential for wakefulness, it makes sense that ATP is produced during sleep. This finding also supports the commonly held notion that sleep is necessary for providing restorative energy.

Part 2 of this book has focused on how the brain controls important functions, ranging from sensory perception to learning to movement to sleep. Part 3 emphasizes how the brain changes over time as we grow and age. The next chapter discusses how the brain controls our reaction to danger, manifested as the "fight or flight" response. In the hectic world in which we live, this response is often experienced as stress. Although stress can set off a cascade of negative physiological reactions, it also can serve as a motivation to take action. Therefore, it is important to understand the difference between good and bad stress.

# Chapter 7: Stress

## In this Chapter



The ability to react quickly in response to threatening events has been with us since the time of our earliest ancestors. In response to impending danger, muscles are primed, attention is focused, and nerves are readied for action — the "fight or flight" response. In today's complex and fast-paced world, stressors are more consistently psychological or socially based, and we face them with less reprieve.

Stress is difficult to define because its effects vary with each individual. Specialists now define stress as any external stimulus that threatens *homeostasis* — the normal equilibrium of body function. Stress also can be induced by the belief that homeostasis might soon be disrupted. Lack or loss of control is a particularly important feature of severe psychological stress, which can have physiological consequences. Most harmful are the chronic aspects of stress.

During the past several decades, however, researchers have found that stress can help the body, too. When confronted with a crucial physical challenge, properly controlled stress responses can provide the extra strength and energy needed to cope. Moreover, the acute physiological response to stress protects the body and brain and helps re-establish or maintain homeostasis. But stress that continues for prolonged periods can repeatedly elevate physiological stress responses or fail to shut them off when they are not needed. When this occurs, the same physiological mechanisms that are helpful can upset the body's biochemical balance and accelerate disease.

Scientists also believe that the individual variation in responding to stress is somewhat dependent on a person's perception of external events. This perception ultimately shapes our internal physiological response. Thus, if we can control our perception of mild to moderate stressors, it may be possible to avoid some of their harmful consequences.

## Immediate Response

A stressful situation activates three major communication systems in the brain, all of which regulate bodily functions. Scientists came to understand these complex systems through experiments, primarily with rats, mice, and nonhuman primates such as monkeys. Scientists then verified the action of these systems in humans.

The first of these systems is the voluntary nervous system, which sends messages to muscles so that we may respond to sensory information. For example, the sight of a shark in the water may prompt people to run from the beach as quickly as possible.

The second communication system is the autonomic nervous system, made up of the sympathetic and the parasympathetic branches. Each of these systems has a specific task in responding to stress. The sympathetic branch causes arteries supplying blood to the muscles to relax in order to deliver more blood, allowing greater capacity to act. At the same time, blood flow to the skin, kidneys, and digestive tract is reduced. The stress hormone epinephrine, also known as adrenaline, is quickly released into the bloodstream. The role of epinephrine is to put the body into a general state of arousal and enable it to cope with the challenge.

In contrast, the parasympathetic branch helps regulate bodily functions and soothe the body once the stressor has passed, preventing the body from remaining in a state of mobilization too long. If these functions are left mobilized and unchecked, disease can develop. Some actions of the calming branch appear to reduce the harmful effects of the emergency branch's response to stress.

The brain's third major communication process is the neuroendocrine system, which also maintains the body's internal functioning. Various stress hormones travel through the blood and stimulate the release of other hormones, which affect bodily processes such as metabolic rate and sexual function.

### The Role of Glucocorticoids

In response to signals from a brain region called the hypothalamus, the adrenal glands secrete glucocorticoids, hormones that produce an array of effects in response to stress. These include mobilizing energy into the bloodstream from storage sites in the body,

increasing cardiovascular tone and delaying long-term processes in the body that are not essential during a crisis, such as feeding, digestion, growth, and reproduction. Some of the actions of glucocorticoids help mediate the stress response, while other, slower actions counteract the primary response to stress and help re-establish homeostasis. Over the short run, epinephrine mobilizes energy and delivers it to muscles for the body's response. The glucocorticoid cortisol, however, promotes energy replenishment and efficient cardiovascular function.

*A stressful situation activates three major communication systems in the brain, all of which regulate bodily functions.*

Glucocorticoids also affect food intake during the sleep-wake cycle. Cortisol levels, which vary naturally over a 24-hour period, peak in the body in the early-morning hours just before waking. This hormone helps produce a wake-up signal, turning on appetite and physical activity. This effect of glucocorticoids may help explain disorders such as jet lag, which results when the light-dark cycle is altered by travel over long distances, causing the body's biological clock to reset itself more slowly. Until that clock is reset, cortisol secretion and hunger, as well as sleepiness and wakefulness, occur at inappropriate times of day in the new location.

Acute stress also enhances the memory of earlier threatening situations and events, increases the activity of the immune system, and helps protect the body from pathogens. Cortisol and epinephrine facilitate the movement of immune cells from the bloodstream and storage organs, such as the spleen, into tissue where they are needed to defend against infection.

Glucocorticoids do more than help the body respond to stress. They also help the body respond to environmental change. In these two roles, glucocorticoids are in fact essential for survival.

## Chronic Stress

What do standing frustrated in a supermarket checkout line or sitting in a traffic jam have in common with fleeing predators, as was done in the early days of human beings? Clearly, these activities are very different, yet they provoke the same responses in the body— the release of hormones (glucocorticoids and epinephrine) to improve memory, boost immune function, enhance muscular activity, and restore physiological balance. Over long periods of time, as these hormones continue to be released, the consequences can be negative: memory is impaired, immune function is suppressed, and energy is stored as fat.

Overexposure to glucocorticoids leads to weakened muscles. Elevated glucocorticoids and epinephrine contribute to hypertension (high blood pressure), atherosclerosis (hardening of the arteries), and abdominal obesity. Epinephrine also increases the release and activity of body chemicals that cause inflammation, adding to the body's chronic stress burden. This continual chemical activity can lead to arthritis and accelerated aging of the brain.

These findings have been verified in animal experiments. Aging rats show impaired neuron function in the hippocampus — an area of the brain important for learning, memory, and emotion — as a result of increased glucocorticoid secretion throughout their lives. Overexposure to glucocorticoids also increases the number of neurons damaged by stroke. Moreover, prolonged glucocorticoid exposure before or immediately after birth causes a decrease in the normal number of brain neurons and smaller brain size.

What's more, scientists have identified a variety of stress-related disorders, including high blood pressure, clogged arteries, impotency and loss of sex drive in males, irregular menstrual cycles in females, colitis, and adult-onset diabetes. Stress also can contribute to sleep loss when people get caught in a vicious cycle: elevated glucocorticoids delaying the onset of sleep, and sleep deprivation raising glucocorticoid levels.

### Different Body Systems Affected

Many different body systems are affected by stress. The immune system receives messages from the nervous system, and it is also sensitive to many of the body's circulating hormones, including stress hormones. Although short-term elevations of stress hormones facilitate immune function and can be

protective against disease pathogens, sustained exposure to glucocorticoids suppresses the immune system, often with negative consequences.

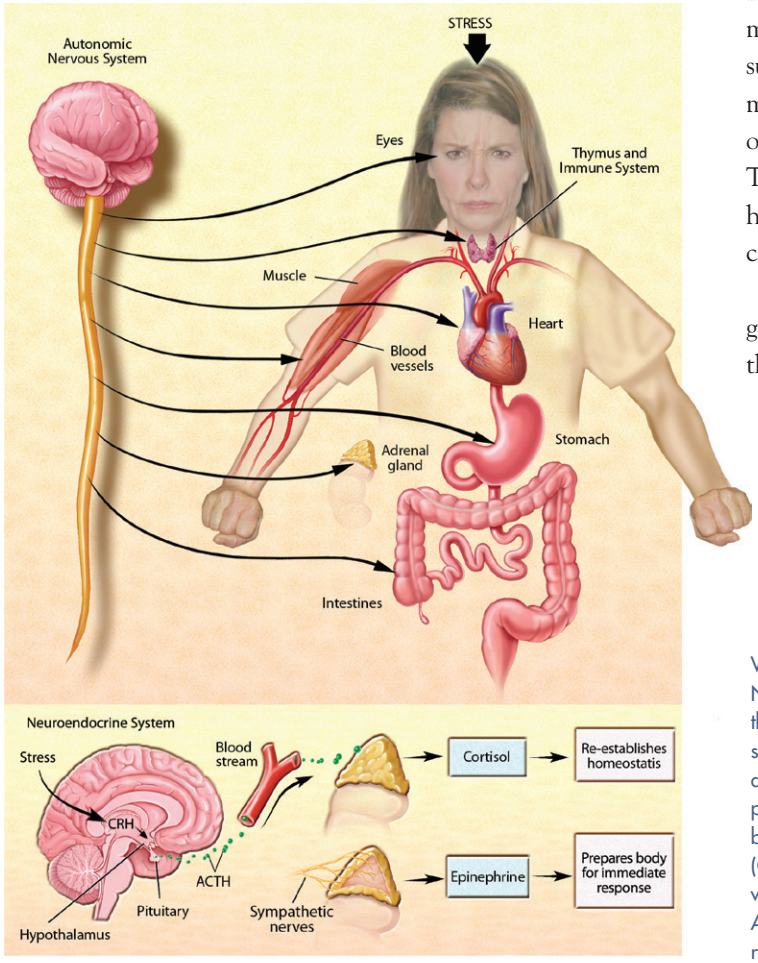
That said, however, glucocorticoid-induced immunosuppression also has its benefits. Normally, glucocorticoids rein in the immune system boost brought on by stress. Without this brake, there is an increased chance of autoimmune disorders caused by an overactive immune system. Such autoimmune disorders occur when the body's immune defenses turn against itself. Then the individual must be treated with synthetic, man-made forms of glucocorticoids (e.g., hydrocortisone and prednisone) in order to keep the immune system in check.

One important determinant of resistance or susceptibility to disease may be a person's sense of control, as opposed to a perceived lack of control or helplessness. This psychological factor may help explain the large individual differences in the physical response to stress. Scientists are actively pursuing this line of research. They are trying to identify how perception of control can alter physiological responses to stress, including the regulation of immune function.

The cardiovascular system also receives messages from the autonomic nervous system, and stressful experiences have immediate and direct effects on heart rate and blood pressure. In the short term, these changes help facilitate a quick response to stressors. But when stressors are chronic and psychological, the effect can be harmful and result in accelerated atherosclerosis and increased risk for heart attack. Research supports the idea that people holding jobs that carry high demands and low control, such as telephone operators, waiters, and cashiers, have higher rates of heart disease than people who can dictate the pace and style of their working lives.

In addition, personality or behavioral type affects an individual's susceptibility to heart attack. People at greatest risk are hostile and irritated by trivial things. One study illustrates this point. Researchers studied two groups of men categorized as having high or low hostility. Both were subjected to harassment. Scientists found that harassed men with high hostility scores had larger increases in levels of stress hormones, muscle blood flow, and blood pressure. Thus, for those people with personality traits that include high levels of hostility, learning to reduce or avoid anger could be important to avoid cardiovascular damage.

Another way that the brain changes over time is by growing older. Chapter 8 explores what we can expect during the normal aging process.




When stress occurs, the sympathetic nervous system is triggered. Norepinephrine is released by nerves, and epinephrine is released by the adrenal glands. By activating receptors in blood vessels and other structures, these substances ready the heart and working muscles for action. Acetylcholine is released in the parasympathetic nervous system, producing calming effects. The neuroendocrine system also maintains the body's normal internal functioning. Corticotrophin releasing hormone (CRH) is released from the hypothalamus and travels to the pituitary gland, where it triggers the release of adrenocorticotropic hormone (ACTH). ACTH travels in the blood to the adrenal glands, where it stimulates the release of cortisol.

# Chapter 8: Aging

## In this Chapter



## Aging in Different Ways

Neuroscientists believe that the brain can remain relatively healthy and full-functioning as it ages. They have concluded that severe declines in memory, intelligence, verbal fluency, and other tasks reflect disease processes; they are not a part of normal aging. Researchers are investigating both the normal and abnormal changes that occur over time and their effect on reasoning and other intellectual activities.

The effects of age on brain function are subtle and very selective. They are not as severe as scientists once thought, and they do not include widespread cell loss. The mistaken belief that pronounced, progressive mental decline is an inevitable part of aging persists for several reasons. Until recently, scientists knew little about how the brain aged. This lack of knowledge applied both to the biology of aging itself as well as to its consequences for brain function. Second, because we are living longer, we have a much larger "sample" of people with normal age-related decline. In 1900, for example, the average life expectancy was about 47 years. At that time, three million people, or 4 percent of the population, were older than age 65, and they were typically in ill health. By 2007, life expectancy reached approximately 78 years, and today, more than 39 million people, or almost 13 percent of the population, are older than age 65.

That said, however, almost everyone gets a bit forgetful in old age, particularly in forming memories of recent events. For example, once most people reach their 70s, they may find themselves forgetting names, phone numbers, and where the car is parked more frequently. In addition, people might respond more slowly to conflicting information. These behaviors are not signs of disease. Rather, they are considered part of the normal aging process. There are, however, a small number of individuals whose mental functioning seems relatively unaffected by age. These people do well throughout life and continue to do well even when they are old, at least until shortly before death. In fact, the wisdom and experience of older people often make up for deficits in performance. The oldest known human, Jeanne Calment, kept her wits throughout her 122-year life span.

Unfortunately, some individuals do develop dementia, a progressive and severe impairment in mental function that interferes with the activities of daily living. The term dementia includes a number of different diseases, of which Alzheimer's disease is the most common. Other dementias include cerebrovascular disease, Pick's disease, and Lewy body disease. Together, the dementias affect as many as 6.8 million people in the U.S, and at least 1.8 million of those cases are severe.

## What We Know — and Don't Know — About Aging

Our best insights into how the normal brain ages come from long-term studies of the nervous system that began decades ago. These are just now bearing results. Coupled with these long-term studies, modern technological advances now make it possible to explore the structure and function of the living brain in more depth than ever before and to ask questions about what actually happens in its aging cells.

We now know that the brain reaches its maximum weight near age 20, and subtle changes in the brain's chemistry and structure begin at midlife for most people. During a lifetime, the brain is at risk for losing some of its neurons, but normal aging does not result in widespread neuron loss. This distinguishes normal aging from the neurodegenerative changes that occurs as part of the disease process in Alzheimer's or Parkinson's disease or after a stroke.

Brain tissue can respond to damage or loss of neurons in several ways. The remaining healthy neurons are able to expand their dendrites and fine-tune their connections with other neurons. If the cell body of the neuron remains

intact, a damaged brain neuron can readjust by inducing changes in its axon and dendrites. Unlike damaged skin or liver, however, a damaged brain cannot respond with a robust generation of new neurons. Relatively small stem cell populations remain in a healthy adult brain, but our current knowledge suggests that they contribute to only a few of the many different types of neurons found, and these neuron types are found in only a few regions of the normal brain. Compounding the problem is the fact that the number of even these stem cells declines as part of the aging process.

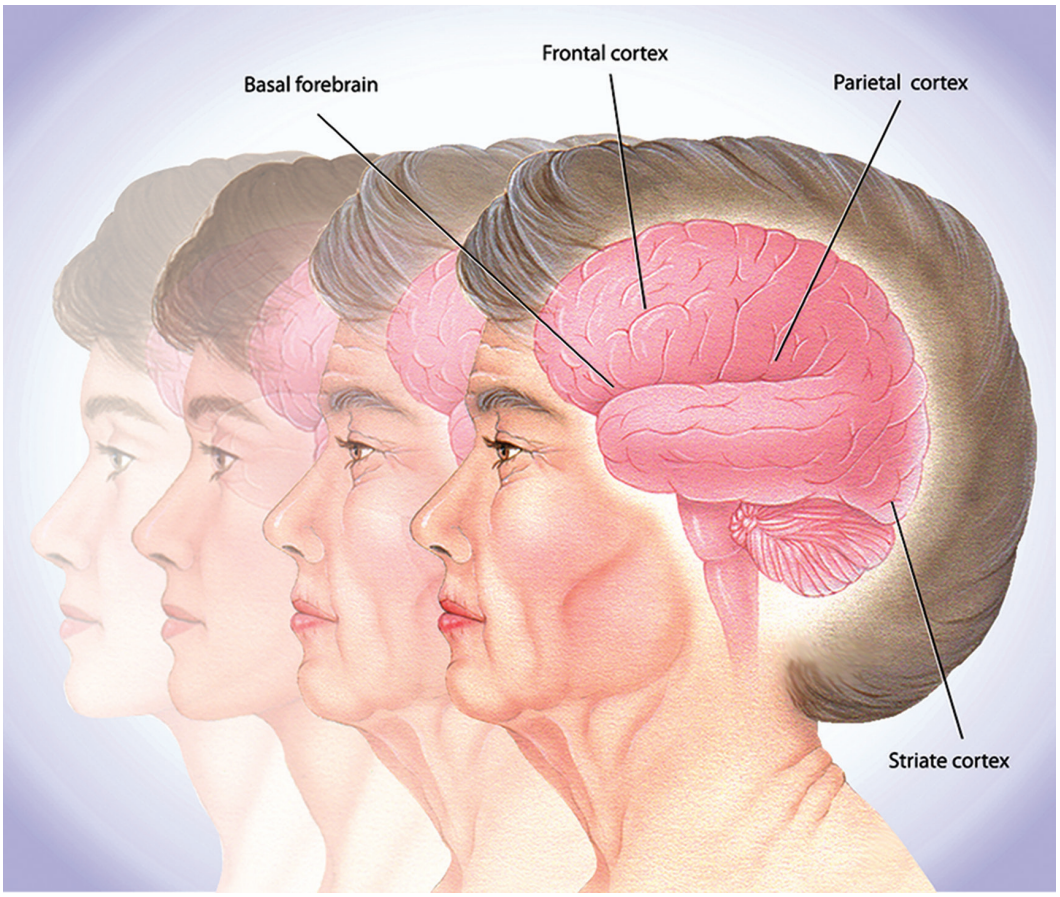
### Changes in Intellectual Capacity

From the first large studies monitoring the mental functioning of the same group of healthy humans over many years, scientists have uncovered unexpected results. They report declines in some mental functions and improvements in others. In several studies, the speed of carrying out certain tasks becomes slower, but vocabulary improves. Other findings demonstrate less severe declines in the type of intelligence relying on learned or stored information compared with the type that depends on the ability to deal with new information.

This research is supported by animal studies in which scientists find that changes in mental function are subtle. For example, in rodents and primates with only minor detectable brain abnormalities, certain spatial tasks, such as navigating to find food, tend to become more difficult with age.

It is also becoming clear that the aging brain is only as resilient as its circuitry. Scientists debate whether this circuitry is changed by neuron atrophy alone or whether some neuron loss over time is inevitable. In any event, when the circuitry begins to break down, remaining neurons can adapt by expanding their roles, and larger portions of the brain can be recruited so that older people can reach performance levels similar to those of younger adults.

In addition, learning conditions may dictate what happens to brain cells. Studies of rats shed light on some of the changes that occur in brain cells when the animals live in challenging, stimulating environments. Middle-aged rats exposed to such environments formed more and longer dendrite branches in the cerebral cortex than did rats housed in isolated conditions. In response




Studies show that many areas of the brain, especially in the cortex, maintain most of their neurons throughout life. The connectivity between neurons changes with aging, indicating that the brain is capable of being modified or improved.

*The brain can remain relatively healthy and full-functioning as it ages.*

to enriched environments, older rats tend to form new dendrite outgrowths and synapses, just as younger animals do. But the response is more sluggish and not as large. Compared with younger rats, older rats have less growth of the new blood vessels that nourish neurons.

Another study showed that when rats were given acrobatic training, their brain cells had more synapses per cell than rats given only physical exercise or rats that were inactive. These findings led scientists to conclude that motor learning generates new synapses. Physical exercise alone, however, improved blood circulation in the brain. In humans, aerobic exercise can also improve cognitive performance.

Despite these advances, most causes of normal brain aging remain a mystery. Dozens of theories abound. One says that specific "aging genes" are switched on at a certain time in life. Another points to the accumulation of genetic mutations or other types of DNA damage. Other researchers implicate hormonal influences or suggest that an immune system gone awry plays a central role in aging. Finally, many researchers advance a theory of brain aging that emphasizes the inexorable accumulation of oxidative damage caused by free radicals, cell byproducts that destroy fats and proteins vital to normal cell function.

As a logical consequence of this uncertainty about what causes normal brain decline, we are equally uncertain about what sustains healthy brain function as we grow older. Increasingly, both physical and mental exercise is viewed as an effective means of slowing the effects of brain aging, perhaps by altering the levels of certain neurotropic factors that are beneficial to brain functioning.

Although much has been learned about the aging brain, many questions remain. For instance, does the production of proteins decline with age in all brain neurons? In a given neuron, does atrophy lead to a higher likelihood of death? How does aging affect gene expression in the brain — the organ with the greatest number of active genes? Do hormonal changes at menopause contribute to gender differences in brain aging?

Neuroscientists, too, speculate that certain genes may be linked to events leading to cell death in the nervous system. By understanding the biology of the proteins produced by genes, scientists hope to be able to influence the survival of neurons and develop ways to improve their functioning.

Our understanding of brain function has evolved over many years of research. Much of this research has been conducted with animals. In recent years, other technologies, such as imaging techniques, have emerged as powerful tools to reveal brain functioning in real time. The next chapter highlights several different ways neuroscientists conduct research and how they have contributed to our knowledge of the brain and the nervous system.

# Chapter 9: Kinds of Research

## In this Chapter

- Animal Research
- Sample Research Methods
- Imaging
- Gene Diagnosis

The field of neuroscience has been built on a foundation of research. This chapter explores three different approaches to research — animal research, imaging techniques, and genomic investigations — and the knowledge that has been gained. These represent a small sample of the ways neuroscientists study the brain.

## Animal Research

Because many animal species are genetically and biochemically similar to humans, animal research has been vital to uncovering the secrets of brain function. In fact, the use of animals has touched every aspect of neuroscience. Without studies with rats and mice, scientists would not have discovered the role of neurotransmitters in cell communication. Other mammals, such as rabbits and cats, have proven to be important models for studies of vision and other senses.

Invertebrates can be used to learn more about the human nervous system. Although the fruit fly's brain is much less complex than that of vertebrates and humans, many features of its nervous system, such as the eye, share striking similarities to humans. Zebrafish, whose fertilized eggs are transparent, have turned out to be good models for developmental neuroscience research. Sea slugs have proven to be important in the study of learning and memory.

Below are a few detailed examples of findings that have emerged from animal research. This research is conducted within national and international guidelines and standards for responsible animal care and use. These guidelines are designed to ensure the humane and appropriate use of animals in all forms of biomedical research.

### Chemical Connections in the Nervous System

Treatments for brain disorders such as Parkinson's disease and *attention deficit hyperactivity disorder* (ADHD) target the synapse. The advances in medicine that led to this type of treatment were made possible by studies using rats and mice. New staining techniques enabled scientists to look at the pathways and connections between different areas of the brain, as well as the neurons that contain and use specific neurotransmitters, so that a roadmap of the brain's connections could be drawn. These techniques were then used in rodents, monkeys, and even in humans who had died to understand more about chemicals and pathways that can be affected by disease, such as the death of neurons containing the neurotransmitter acetylcholine in Alzheimer's disease.

Knowledge about another neurodegenerative disease, Parkinson's disease, has emerged through studies with rabbits and mice. These experiments, conducted by Nobel Laureate Arvid Carlsson, revealed that the neurotransmitter dopamine was being depleted. Using pigeons, scientists then discovered that this neurotransmitter was highly concentrated in the basal ganglia, the part of the brain involved in motor function. From there, researchers concluded that Parkinson's disease causes cells in the basal ganglia to die, limiting the production of dopamine. This finding led to the discovery of the first treatment for Parkinson's — a drug called levodopa, which is converted to dopamine in brain cells.

Rats have proven to be helpful in uncovering changes to the brain as a result of *drug addiction*. The first step in this work was determining whether nonhuman species could become addicted to drugs. Experiments showed that when rats were given free access to the same drugs that humans become addicted to, they will also take these drugs compulsively. Further studies showed that the part of the brain affected by drugs is the reward pathway, especially

the dopamine neurons of the ventral tegmental area, which communicates with the nucleus accumbens. As shown in rats — and consistent with what happens in humans — this pathway is also activated by natural rewards, such as food, water, and sex, but drugs of abuse can take over the reward system by mimicking or blocking the function of neurotransmitters.

Other animal studies have shown that drugs of abuse can affect brain systems concerned with learning and memory; as a result, cues or habits associated with taking drugs can elicit a craving for that drug, even after long periods of abstinence. These findings are helping scientists understand how changes in the brain can lead to addiction and why some people are more likely to become addicted than others. This work, of which animal research is a crucial part, has enabled researchers to develop treatments for addiction.

### Learning and Memory

In his work on learning and memory, Nobel Laureate Eric Kandel began his investigations using mammals, but soon found they were too complex to enable him to study basic memory processes. So he turned to a simpler organism — the sea slug—and was successful in uncovering how short- and long-term memories are retained.

Kandel found that certain stimuli resulted in a more robust protective reflex, a form of learning for the sea slug. Furthermore, the strengthened reflex could remain in place for days and weeks as a short-term memory. Additional work showed that a stronger synapse was responsible for the retention of this information.

Researchers have learned a great deal about the basis of behavior by studying animal models, including the fruit fly *Drosophila melanogaster*. [Credit: Edward Kravitz, PhD, Harvard Medical School]

Long-term memories form in a different way. Stronger stimuli activate genes, resulting in an increase of some proteins and a decrease in others. These changes ultimately lead to the growth of new synapses. After demonstrating that both short- and long-term memory in sea slugs involve the synapse, Kandel was able to illustrate that similar mechanisms are at work in mice and other mammals.

### Understanding Critical Periods

Animal studies led to the understanding of the concept of critical periods in the development of vision. Experiments with monkeys and cats helped determine that treatment for amblyopia, a condition in which the vision of one eye is greatly reduced because the eyes do not work well together, has the best outcome when it is started early in life, before the age of eight. During this period of time, visual experiences guide the development of the visual circuits. After the critical period comes to an end, the circuits cannot be easily modified. These animal studies showed the importance of the critical period in modifying visual circuits, leading to the realization that there is currently no cure for amblyopia in adults. For this work, neuroscientists David Hubel and Torsten Wiesel won the Nobel Prize in 1981.

More recently, studies with mice are starting to reveal what factors change in the brain to prevent rewiring after a certain age. Modifying or removing these factors seems to allow for changes in vision later in life. This has been borne out in the lab, where vision has been restored in older amblyopic mice. Scientists hope that these experiments can be applied to humans, resulting in a cure for adults with this condition.

## Sample Research Methods

Psychologists, chemists, geneticists, computer scientists, and physicists can all study the brain. Because neurons communicate by both chemical and electrical means, many researchers study these properties and how they are affected by experience or disease. A variety of techniques make these studies possible.

For example, researchers use a technique called microdialysis to measure the amount of a particular brain chemical found in a specified area of the brain. Following the discovery that chemicals and other molecules are transported within neurons, methods have been developed to visualize brain activity and precisely track nerve fiber connections within an animal's nervous system. This can be done by injecting a radioactive amino acid into brain cells,

allowing activities in the nervous system to show up on film. In another technique, the enzyme horseradish peroxidase is injected and taken up by nerve fibers that later can be identified under a microscope.

The study of the electrical properties of neurons is called electrophysiology. The discovery of action potentials, the way neurons communicate, and long-term potentiation, the cellular event that makes learning and memory possible, both relied on this technique.

Electrophysiology is now being used to study the human brain and even to diagnose some conditions, such as hearing loss. This function is assessed in infants through electrophysiological recordings of auditory brainstem responses to sound. During this procedure, electrodes are placed on specific parts of the head, which make recordings that are then processed by a computer. The computer makes an analysis based on the time lapse between stimulus and response. It then extracts this information from background activity. Similarly, in EEG, electrodes placed around the head record electrical activity of the human brain in response to a variety of stimuli and activities.

These are examples of research techniques developed on animals that are now being used to study and even diagnose humans. Similarly, brain imaging techniques have allowed detailed examination of the human brain.

## Imaging

### Positron Emission Tomography (PET)

PET is one of the most important techniques for measuring blood flow or energy consumption in the brain. This method of measuring brain function is based on the detection of radioactivity emitted when positrons, positively charged particles, undergo radioactive decay in the brain.

Small amounts of a radioisotope are introduced into the blood, which then carries the radioisotope to different brain areas. The radioisotope shows up in the brain in proportion to how hard local neurons are working. Computers build three-dimensional images of changes in blood flow based on the amount of radiation emitted in different brain regions. The more brain activity, the more vivid the picture that is created.

PET studies have helped scientists understand more about how drugs affect the brain and what happens while people are working on different activities, such as learning and using language. PET studies also have been helpful in understanding certain brain disorders, such as stroke, depression, and Parkinson's disease. For example, PET allows scientists to measure changes in the release of some neurotransmitters. This information can be used to pinpoint the relationship between a particular neurotransmitter and a behavior or cognitive process. Within the next few years, PET could enable scientists to identify the biochemical nature of neurological and mental disorders and to determine how well therapy is working in patients. Already, PET has revealed marked changes in the depressed brain. Knowing the location of these changes helps researchers understand the causes of depression and monitor the effectiveness of specific treatments.

Another technique, single photon emission computed tomography (SPECT), is similar to PET, but its pictures are not as detailed. SPECT is much less expensive than PET because the tracers it uses break down at a slower rate and do not require a nearby particle accelerator, typical of those used in nuclear physics, to produce them.

### Magnetic Resonance Imaging (MRI)

Providing a high-quality, three-dimensional image of organs and structures inside the body without X-rays or other radiation, *MRIs* are noninvasive and unsurpassed in the anatomical detail they show. MRIs tell scientists when structural abnormalities first appear in the course of a disease, how they affect subsequent development, and precisely how their progression correlates with mental and emotional aspects of a disorder. In some instances, they can even reveal minute changes that occur over time.

During the 15-minute MRI procedure, a patient lies inside a massive, hollow, cylindrical magnet and is exposed to a powerful, steady magnetic field. Different atoms in the brain resonate to different frequencies of magnetic fields. A background magnetic field lines up all the atoms in the brain. Then a second magnetic field, oriented differently from the background field, is turned on and off many times a second; at certain pulse rates, particular atoms resonate to and line up with this second field. When the second field is turned off, the atoms that were lined up with it swing back to align with the background field. As they swing back, they create a signal that can be picked up and converted into an image. Tissue that contains a lot of water and fat produces a bright image; tissue that contains little or no water, such as bone, appears black.

A different MRI procedure can also assess the path of fiber tracts in the brain; that is, the connectivity between

regions. This technology, referred to as diffusion tensor imaging, takes advantage of diffusion rates of water, which tend to be higher along fiber tracts, to produce high-resolution images of how areas may connect in the brain.

MRI images can be constructed in any plane, and they are particularly valuable in studying the brain and spinal cord. The images reveal the precise extent of tumors rapidly and vividly and provide early evidence of potential damage from stroke, allowing physicians to administer proper treatments early, when they can have an impact.

### Magnetic Resonance Spectroscopy (MRS)

*MRS*, a technique related to MRI, uses the same machinery but measures the concentration of specific chemicals — such as neurotransmitters — in different parts of the brain instead of blood flow. MRS also holds great promise: By measuring the molecular and metabolic changes that occur in the brain, this technique has already provided new information about brain development and aging, Alzheimer's disease, schizophrenia, autism, and stroke. Because it is noninvasive, MRS is ideal for studying the natural course of a disease or its response to treatment.

Magnetic resonance imaging is a powerful technique to examine the structure and observe the function of the human brain.

### Functional Magnetic Resonance Imaging (fMRI)

One of the most popular neuroimaging techniques today is fMRI. This technique compares brain activity under resting and active conditions. It combines the high-spatial resolution, noninvasive imaging of brain anatomy offered by standard MRI with a strategy for detecting increases in blood oxygen levels when brain activity brings fresh blood to a particular area of the brain — a correlate of neuronal activity. This technique allows for more detailed maps of brain areas underlying human mental activities in health and disease. To date, fMRI has been applied to the study of various functions of the brain, ranging from primary sensory responses to cognitive activities. Given fMRI's temporal and spatial resolution, as well as its noninvasive nature, this technique is often preferred for studies investigating dynamic cognitive and behavioral changes.

**Magnetoencephalography (MEG)** *MEG* is a recently developed technique that reveals the source of weak magnetic fields emitted by neurons. An array of cylinder-shaped sensors monitors the magnetic field pattern near the patient's head to determine the position and strength of activity in various regions of the brain. In contrast with other imaging techniques, MEG can characterize rapidly changing patterns of neural activity — down to millisecond resolution — and can provide a quantitative measure of the strength of this activity in individual subjects. Moreover, by presenting stimuli at various rates, scientists can determine how long neural activation is sustained in the diverse brain areas that typically respond.

One of the most exciting developments in imaging is the combined use of information from fMRI and MEG. The former provides detailed information about the areas of brain activity while an individual is engaged in a particular task, whereas MEG tells researchers and physicians when certain areas become active. Together, this information leads to a much more precise understanding of how the brain works in health and disease.

**Optical Imaging and Other Techniques** Optical imaging relies on shining weak lasers through the skull to visualize brain activity. These techniques are inexpensive and relatively portable. They are also silent and safe: Because only extremely weak lasers are used, these methods can be used to study everyone, even infants. In a technique called near infrared spectroscopy (NIRS), technicians shine lasers through the skull at near infrared frequencies, which renders

the skull transparent. Blood with oxygen in it absorbs different frequencies of light from blood in which the oxygen has been consumed. By observing how much light is reflected back from the brain at each frequency, researchers can track blood flow. Diffuse optical tomography is then used to create maps of brain activity.

A similar technique, the event-related optical signal, records how light scatters in response to rapid cellular changes that arise when neurons fire, potentially assessing neural activity lasting milliseconds. Another technique, called transcranial magnetic stimulation (TMS), works by inducing electrical impulses in the brain. This is accomplished by altering magnetic fields through the use of an electromagnetic coil that emits powerful magnetic pulses while held against the scalp. Repetitive TMS is being used to investigate the role of specific brain regions during behavior, and it can be combined with other neuroimaging techniques. For example, when TMS is used with fMRI, a functional correlation between a region and a behavior can be established.

## Gene Diagnosis

Genes form the blueprint, or set of instructions, needed for our bodies to grow and function. They consist of short sections or sequences of deoxyribonucleic acid (DNA) bases represented by the letters A, C, G, and T. DNA strands are often visualized as long, spiraling, double-helix structures found within the 23 pairs of chromosomes in every human cell. The exact number of human genes is uncertain and the functions of many genes are still unknown, but the current estimate is that humans have approximately 20,000–25,000 pairs of genes contained in these 23 chromosomes. Humans inherit one copy of each gene from the mother and one from the father and then pass down one copy of each of their genes to their children. Thus, genes and their corresponding traits are passed down through families.

More than 7,000 disorders, including many that affect the brain and neurodevelopment, are suspected to have a genetic basis. These problems occur because changes in the DNA, such as "misspellings" in the gene instructions or incorrect amounts of DNA, can prevent a gene from functioning properly. These changes are called mutations. As a result, DNA changes contribute to disease, and mutations in genes important for brain development and function can cause a wide variety of neurological and psychiatric conditions.

Genetic linkage studies, which studied families and large groups of unrelated people diagnosed with specific conditions, made it possible to find the chromosomal location of many genes. Newer techniques, called chromosome microarrays, look carefully at the overall chromosome makeup of a person and find out if segments of chromosomes, perhaps involving multiple genes, are missing (called deletions) or present in more than the usual amount (called duplications). Microarrays have recently helped identify many types of rearrangements of chromosome structure and specific genes that are associated with developmental disabilities and neurological disorders.

Knowing such genetic information can clarify diagnoses and improve understanding of the cause of symptoms, allowing physicians to optimize methods of prevention and treatment. This knowledge can also help individuals understand the chance of a condition affecting other members of their family and allow for prenatal testing and carrier status evaluations. In some cases, genetic analysis can even be helpful in evaluating the malignancy of specific tumors and reactions to certain medications and treatments.

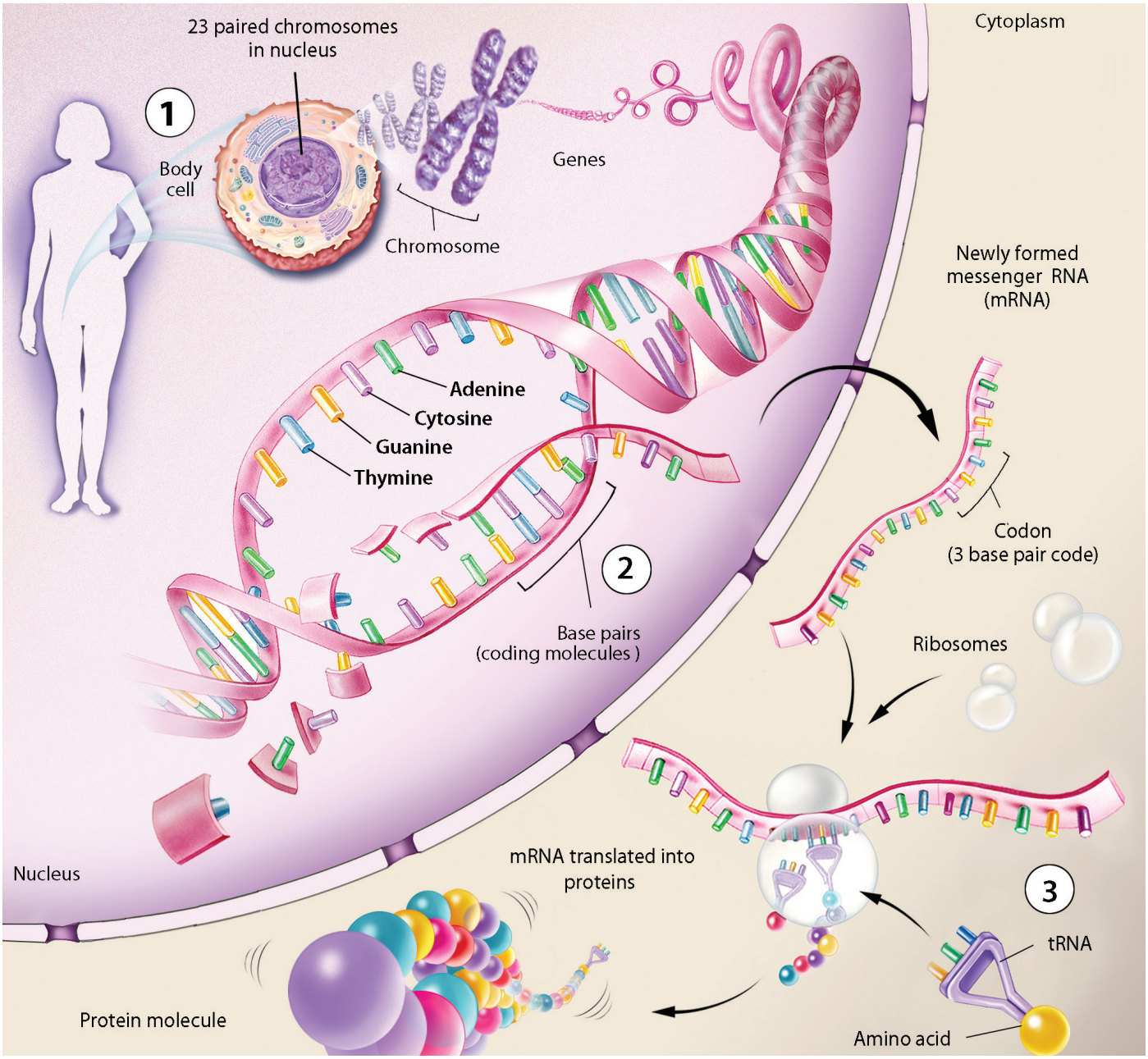
### Tracking down Genes

Early mapping techniques allowed scientists to track down the genes responsible for several neurological conditions. These include *HTT*, the gene that is altered in patients diagnosed with Huntington's disease; *RB1*, which causes inherited retinoblastoma, a rare, highly malignant, childhood eye tumor that can lead to blindness and death; and the X-linked gene *DMD*, responsible for Duchenne muscular dystrophy, a progressive muscle disease. In some cases, mapping techniques have shown that one condition may actually be due to mutations in any one of a group of genes. This is the situation with a condition called Walker-Warburg syndrome, which causes severe problems involving the brain, eyes, and muscles, leading to death in infancy or early childhood. Thus far, at least five genes are known to be associated with this disease, with still others yet to be discovered.

Many forms of intellectual disability, previously referred to as mental retardation, are also due to genes that are not working properly. Gene mapping enabled doctors to find the *FMR1* gene, which is abnormal in people diagnosed with fragile X syndrome, the most common cause of inherited intellectual disability in males. *FMR1* is located on the X chromosome and is important for neuronal communication. Other groups of scientists are also investigating whether there are genetic components to schizophrenia, *bipolar disorder*, and

alcoholism, but to date, their findings are not conclusive. For instance, people missing a certain segment of chromosome 22, due to 22q deletion syndrome, have a higher chance of developing mental illness. However, not all people with this chromosome deletion develop mental illness, nor do all people with mental illness have such a genetic finding.

Rarely, genes passed down from parents can undergo changes very early in fetal development so that a child might have a genetic alteration that is not found in either of his parents. In these cases, the child could have a genetic condition that may potentially be passed on to offspring but was not necessarily inherited from his parents. For example,




Every trait and chemical process in the body are controlled by a gene or group of genes on 23 paired chromosomes in the nucleus of every cell (1). Each gene is a discrete segment along the two tightly coiled strands of DNA that make up these chromosomes. DNA strands have four different types of coding molecules — adenine (a), cytosine (C), guanine (g), and thymine (T) — the sequence of which contains the instructions for making all the proteins necessary for life (2). During protein production, a gene uses a molecule called mRNA to send a message with instructions for the amino acids needed to manufacture a protein (3).

scientists have identified a gene called *LIS1* that helps tell the brain how to grow. People with mutations in the *LIS1* gene have smoother brains than normal and may have seizures. In addition, severe intellectual disability is common. However, the parents of these individuals do not have mutations in their *LIS1* genes, so there is a very low chance of other children of those parents having the same diagnosis.

*Genes form the blueprint, or set of instructions, needed for our bodies to grow and function.*

Importantly, a great deal of effort has been put into better understanding the genetic basis of autism. Many genetic changes have been associated with autism, or more specifically, with conditions that can include autism or autism-like features as symptoms. Such conditions include tuberous sclerosis complex, due to mutations in the genes *TSC1* and *TSC2*, as well as Rett syndrome, associated with the *MECP2* gene. Chromosome abnormalities identified through microarray technology have also been associated with autism. Deletions of a certain portion of chromosome 16 can lead to a variety of neurological symptoms, including autism in some individuals. However, at this point in time no one gene or set of genes can be attributed to the majority of autism diagnoses. Therefore, significant research efforts continue, with the goal of better understanding genetic contributions to autism spectrum disorders.

Overall, our understanding of the structure and function of individual genes associated with diseases of the brain and nervous system is progressing rapidly. Once genes are implicated in a disease process and it is known who carries certain gene variants, it becomes theoretically possible to develop targeted therapies for specific conditions. There are now very early interventional studies for some neurological conditions, such as Angelman syndrome and tuberous sclerosis complex. However, much remains to be learned about these and other conditions before cures might emerge. For instance, it is still largely unknown why different people who carry mutated versions of the same gene, even within a family, can have different types or degrees of symptoms, or sometimes no symptoms at all.

A new DNA sequencing technology, often referred to as "next generation" sequencing, offers great hope for uncovering the genetic basis of many neurological conditions. But this technology also comes with many challenges, not the least of which is the enormous volume of data it promises to produce. This testing is expected to uncover the functional sequence of all 20,000 or more human genes (collectively called the exome) as well as the remaining associated DNA that is thought to influence or regulate these genes (together with the exome, this is called the genome) for each person studied. So far, such studies have revealed numerous types of genetic variants, making for more variability in human genes than initially recognized.

Interpreting so many DNA variants at once, and knowing which ones are truly associated with a disease under study, is a complex and daunting task. Nevertheless, this next generation of sequencing has already led to the identification of the *MLL2* gene responsible for Kabuki syndrome, which causes congenital intellectual disabilities along with certain abnormal facial features. Despite being a distinctive condition, Kabuki syndrome long escaped efforts to identify its genetic underpinnings. This is only one example of the many expected genetic discoveries that will result from evolving methods and techniques for studying the genetics of the nervous system and conditions causing human disease.

This chapter has focused on the tools of neuroscience, with a focus on animal research, imaging, and gene diagnosis. In Part 5, the emphasis in Chapters 10 through 14 is on different kinds of neurological and psychiatric diseases and disorders. In addition to explaining these disorders, in many instances, information is given about which tools have helped neuroscientists unravel the mystery surrounding each one.

# Chapter 10: Childhood Disorders

## In this Chapter



## Autism

Autism spectrum disorders (ASD) are characterized by impaired social skills; verbal and nonverbal communication difficulties; and narrow, obsessive interests or repetitive behaviors. Common associated symptoms include intellectual disabilities, seizures, and gastrointestinal problems. One of every 110 babies born in the United States, approximately 40,000 new cases each year, is diagnosed with ASD, an incidence far greater than in the 1970s. This increase is due, in part, to changes in diagnostic criteria, detection of subtler forms of autism, and enhanced parent and clinician referral based on greater awareness. Mounting evidence, however, indicates that there is a true increase in the number of children with autism. As a result, research efforts are now focusing on the interplay between genetic and environmental components that might contribute to the diagnosis.

Based mainly on twin studies, ASDs are thought to be highly genetic; already, more than 100 genes have been linked to increased risk for autism. That said, however, there is currently no single genetic or biochemical biomarker specifically for autism, because no single gene mutation or biological change will predict the disorder. Therefore, at this time, there is no way to determine if a newborn child is at risk for autism.

For this reason, ASD is typically diagnosed based on behavioral symptoms detected in children about three years of age. However, very sensitive measures of social engagement and interaction can detect differences in children between one and two years old, a time when many affected children exhibit abnormal, accelerated growth of the brain. This abnormal growth may indicate that brain development has gone awry, thus making it a potential marker for early evaluation. In addition, recent evidence indicates that some forms of autism may be due to dysregulation of the immune system, either in the mother or the child. One day, genetic or other biological tests may complement behavioral indicators to allow earlier diagnosis and intervention, as well as the means to possibly prevent or reduce ASD symptoms.

Brain alterations in autism are subtle; there is no obvious change such as in Down syndrome or Alzheimer's disease. There is speculation that abnormal development of certain regions of the brain involved in language, cognition, and social communication leads to abnormal connections with other parts of the brain.

Although no cure exists and no drugs for the major symptoms of autism have been developed, many affected children respond very well to specialized behavioral therapies based on learning theory, with earlier interventions leading to better outcomes. Many of the therapeutic approaches to autism are guided by an increased understanding of how the brain normally reacts to learning, bonding, and social challenge as it develops.

One final note: It is now recognized that many of the brightest and most creative individuals in history may have had subtle forms of ASD. Therefore, researchers and others working in the field need to be aware that some "higher functioning" people with autism do not want to be "cured." Instead, they would like to be accepted for who they are.

## Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) was first described more than 100 years ago. Characterized by excessively inattentive, hyperactive, or impulsive behaviors, ADHD affects an estimated 5 to 8 percent of school-age children. Studies show that as many as 60 percent of these children will continue to experience ADHD symptoms as adults. Children with ADHD are more likely to have

problems in school, graduating from high school, maintaining a job, abusing drugs, or having healthy relationships.

Symptoms of ADHD appear by middle childhood, last for six months or longer, and impair normal functioning to a significant degree in the following settings: for children — at school, among friends, and at home; for adults — at work and at home. Currently, no objective diagnostic test for ADHD exists. Diagnosis requires a comprehensive evaluation, including a clinical interview, parent and teacher ratings for children, and self and other ratings for adults. Learning disorder and psychological testing may also be used to clarify if other disorders are present along with the ADHD or if other conditions that look like ADHD may be responsible for the behaviors in question. Thorough evaluation is required because problems with attention can be triggered by many other conditions; in particular, adults may have attention issues along with other disorders such as depression.

Twin and family studies show that ADHD has a strong genetic influence, and genes encoding components of dopamine and norepinephrine transmission have been implicated. Increasingly, studies are finding correlations between ADHD and differences in brain function. Altered activity is often observed in circuits connecting the cortex, the striatum, and the cerebellum, particularly in the right hemisphere. Recent studies show a delay in cortical development in some children with ADHD, although most individuals with ADHD do not outgrow the disorder as they mature. Rather, their symptoms often change as they grow older, with less hyperactivity as adults. Problems with attention tend to continue into adulthood.

Recent imaging studies have shown reduced catecholamine transmission in at least some patients with this disorder. Because prefrontal circuits require an optimal level of catecholamine stimulation, reduced catecholamine transmission could lead to weakened prefrontal cortical regulation of attention and behavior and symptoms of ADHD.

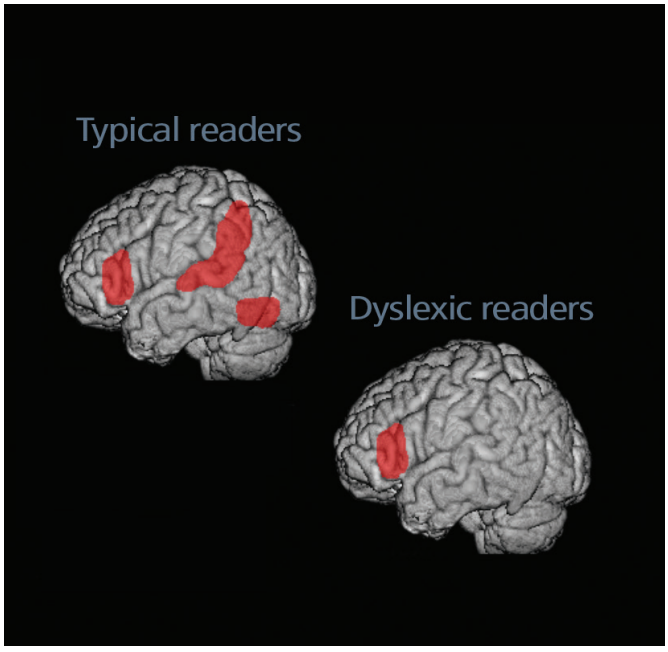
ADHD is commonly treated with parent education, school-based interventions, and medications such as stimulants (e.g., methylphenidate) and newer, nonstimulant drugs. Adults benefit from the same medications as children and may find some behavioral therapies helpful. The medications all act by enhancing catecholamine transmission.

There is no cure for ADHD at this time. Treatment effectiveness should be re-evaluated in each person on a regular basis to determine if the current treatment continues to be optimal.

## Down Syndrome

*Down syndrome*, the most frequently occurring chromosomal condition, appears in 1 of every 691 babies, or about 6,000 babies annually in the United States. It typically occurs when, at the time of conception, an extra copy of chromosome 21 — or part of its long arm — is present in the egg or, less commonly, in the sperm. It is not known why this error occurs, and it has not been linked to any environmental or behavioral factors, either before or during pregnancy, but the risk is markedly increased with the age of the mother. At age 25, the risk is about 1 in 1,250 births; at age 40, it is 1 in 100. Because of higher fertility rates in younger women, 80 percent of children with Down syndrome are born to women under 35 years of age. Prenatal screening tests, such as the triple and quadruple screen blood tests, can accurately detect Down syndrome in about 70 percent of fetuses. Definitive prenatal diagnoses can be obtained with either chorionic villus sampling or amniocentesis.

Down syndrome is associated with approximately 50 physical and developmental characteristics. An individual with Down syndrome is likely to possess, to various degrees, some of these characteristics: mild to moderate intellectual disabilities; low muscle tone; an upward slant to the eyes; a flat facial profile; an enlarged tongue; and an increased risk of congenital heart defects, respiratory problems, and digestive tract obstruction.




Brain-imaging studies show differences in the dyslexic brain during reading tasks. [Credit: Guinevere Eden, DPhil, Georgetown University.]

By age 40, nearly all people with Down syndrome show some neurological changes similar to those seen in Alzheimer's disease, and most show cognitive decline by age 60.

Babies with Down syndrome develop much as typical children do but at a somewhat slower rate. Just as their peers do, they learn to sit, walk, talk, and toilet train. Early intervention programs can begin shortly after birth and can help foster an infant's development.

Thanks to medical advances and a greater understanding of the potential of those with this condition, people with Down syndrome have been able to have longer and fuller lives. They are being educated in their neighborhood schools, participating in community activities, and finding rewarding employment and relationships.

Although there is no cure for Down syndrome or means of preventing it, scientists are moving closer to understanding the role that the genes on chromosome 21 play in a person's development. There are several mouse models of Down syndrome that are allowing scientists to focus on molecular factors important in the condition. Once this mystery is understood, researchers hope to decode the biochemical processes that occur in Down syndrome and learn how to treat or cure this disorder.

## Dyslexia

An estimated 8 to 10 percent of children in the United States have some form of learning disability involving difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning, or mathematical abilities. These problems often occur in people with normal or even high intelligence.

Dyslexia, a specific reading disability, is the most common and most carefully studied of the learning disabilities. It affects 80 percent of all those identified as learning disabled, or as many as 15 to 20 percent of Americans. Dyslexia is characterized by an unexpected difficulty in speaking and reading in children and adults who otherwise possess the intelligence, motivation, and schooling considered necessary for accurate and fluent reading. Studies indicate that although there can be improvement, dyslexia is a persistent, chronic condition.

There is now a strong consensus that the central difficulty in most forms of dyslexia reflects a deficit within the language system — more specifically, in a component of the language system called phonology. This deficit results in difficulty in both oral language and reading. There may be mispronunciations of words, lack of fluency in speech, hesitations before responding, and word retrieval difficulties. As a result, a person with dyslexia often needs time to summon a verbal response when questioned.

As children approach adolescence, one manifestation of dyslexia may be a very slow reading rate. Children may learn to read words accurately, but their reading will not be fluent or automatic, reflecting the lingering effects of a phonologic deficit. Because they can read words accurately — albeit very slowly — dyslexic adolescents and young adults may mistakenly be assumed to have "outgrown" their dyslexia. The ability to read aloud accurately, rapidly, and with good expression, as well as facility with spelling, may be most useful clinically in distinguishing students who are average from those who are poor readers. In some languages that are more consistent in the relationship between letters and sounds, such as Finnish and Italian, slow reading may be the only manifestation of dyslexia at any age.

A range of investigations indicates that there are differences in brain regions between dyslexic and nonimpaired readers involving three important left hemisphere neural systems, two posteriorly (parieto-temporal, occipito-temporal) and one anteriorly around the left inferior frontal region (*Broca's area*). Converging evidence derived from functional brain imaging indicates that dyslexic readers demonstrate a functional inefficiency in an extensive neural system in the posterior portion of the brain. The brain images that result from these studies are referred to as the neural signature of dyslexia.

It is clear that dyslexia runs in families, but initial hopes that dyslexia would be explained by one or just a few genes have not been realized. Genome-wide association studies (GWAS) in dyslexia have so far identified genetic variants that account for only a very small percentage of the risk — less than 1 percent — making it unlikely that a single gene or even a few genes will identify people with dyslexia. Current evidence suggests that dyslexia is best conceptualized within a multifactorial model, with multiple genetic and environmental risk and protective factors leading to dyslexia.

Interventions to help children with dyslexia focus on teaching the child that words can be segmented into smaller units of sound and that these sounds are linked with specific letter patterns. In addition, children with dyslexia require practice in reading stories, both to allow them to apply their newly acquired decoding skills to reading words in context and to experience reading for meaning and enjoyment.

# Chapter 11: Addiction

## In this Chapter

- Nicotine
- Alcohol
- Marijuana
- Opiates
- Psychostimulants
- Club Drugs

Drug abuse is one of the nation's most serious health problems. About 9 percent of Americans, more than 22 million people, abuse drugs on a regular basis. Drug abuse, including alcohol and nicotine, is estimated to cost the United States more than $600 billion each year.

If continued long enough, drug abuse can eventually alter the very structure and chemical makeup of the brain, producing a true brain disorder. This disorder is called drug addiction or drug dependence. Drug addiction is characterized by a pathological desire for drugs, such that drug-seeking and drug-taking behaviors occupy an inordinate amount of an individual's time and thoughts, at the expense of other activities. These behaviors persist despite many adverse consequences. Addiction is also characterized by difficulty controlling frequency of use and terminating use, despite a stated desire to do so.

People initially experiment with drugs for many different reasons, a key one being that most drugs of abuse produce feelings of pleasure or remove feelings of stress and emotional pain. Neuroscientists have found that almost all abused drugs produce pleasure by activating a specific network of neurons called the brain reward system. The circuit is normally involved in an important type of learning that helps us stay alive. It evolved to mediate the pleasurable and motivating effects of natural rewards, such as eating when we are hungry or drinking when we are thirsty. Indeed, when a reward produces feelings of pleasure, we learn to repeat the actions that got us the reward in the first place. Drugs can activate this same system, thus promoting continued drug use.

Neuroscientists have learned a great deal about how drugs of abuse affect neurons to exert their influence. Abused drugs alter the ways neurotransmitters carry their messages from neuron to neuron. Some drugs mimic neurotransmitters, while others block them. Still others alter the way neurotransmitters are released or inactivated. Ultimately, in all cases, the brain reward system is activated inappropriately because drugs alter the chemical messages sent among neurons in this circuit.

Finally, neuroscientists have learned that addiction requires more than the activation of the brain reward system. Over the past 20 years or so, research has indicated that the drugs themselves change the brain of susceptible individuals in complex ways, leading to symptoms of addiction. In addition to the brain reward system, brain regions that are changed by drugs include those involved in executive functions and judgment. These latter brain systems are important in inhibiting behavior and in decision-making.

The process of becoming addicted is influenced by many factors that scientists are only beginning to understand. Motivation for drug use is an important one. For example, people who take opioids to get high may get addicted, but people who use them properly to relieve pain rarely do. Genetic susceptibility and environmental factors, such as stress, can alter the way that people respond to drugs. The characteristics of the drugs themselves, such as how quickly they enter the brain, also play a role in addiction. In addition, the development of tolerance — the progressive need for a higher drug dose to achieve the same effect — varies in different people, as does drug dependence — the adaptive physiological state that results in withdrawal

symptoms when drug use stops. Tolerance and dependence are standard responses of the brain and body to drugs. At the same time, the individual is starting to feel that it is impossible to live without a drug. When this feeling starts to grow, it means that the person is developing a motivational form of dependence as well.

An important question for addiction research is to understand how these many factors interact to predispose individuals to addiction. The hope is that the knowledge and insight into abuse and addiction that emerge from this research will lead to new therapies.

## Nicotine

In 2009, more than 70 million Americans smoked. Despite definitive proof that smoking can be fatal, nicotine still is one of the most widely abused substances. In fact, tobacco kills more than 440,000 U.S. citizens each year — more than alcohol, cocaine, heroin, homicide, suicide, car accidents, and HIV combined. Tobacco use is the leading preventable cause of death in the United States. The overall cost of smoking in the United States is estimated to be $193 billion each year. Nicotine, the addicting substance in tobacco, acts through the well-known acetylcholine nicotinic receptor. This drug can act as both a stimulant and a sedative. Nicotine stimulates the adrenal glands, and the resulting discharge of *epinephrine* causes a "kick" — a sudden release of glucose paired with an increase in blood pressure, respiration, and heart rate. In addition, nicotine releases dopamine in the brain regions that control motivation, which is one reason that people continue to smoke.

Much better understanding of addiction, coupled with the identification of nicotine as an addictive drug, has been instrumental in the development of treatments. Nicotine gum, the transdermal patch, nasal spray, and inhalers are equally effective in treating the more than one million people addicted to nicotine. These techniques are used to relieve withdrawal symptoms and are helpful in that they produce less severe physiological alterations than using tobacco products. They generally provide users with lower overall nicotine levels than they receive with tobacco and totally eliminate exposure to smoke and its deadly contents.

The first non-nicotine prescription drug, bupropion, an antidepressant, has been approved for use as a pharmacological treatment for nicotine addiction. An exciting advance is the use of varenicline for smoking cessation. This medication interacts directly with the acetylcholine nicotinic receptor in a key part of the brain's reward circuitry and prevents nicotine from activating this circuit. The development of varenicline is a prime example of how basic science research can lead to the production of novel medications. Behavioral treatments also are important in helping an individual learn coping skills for both short- and long-term prevention of relapse.

## Alcohol

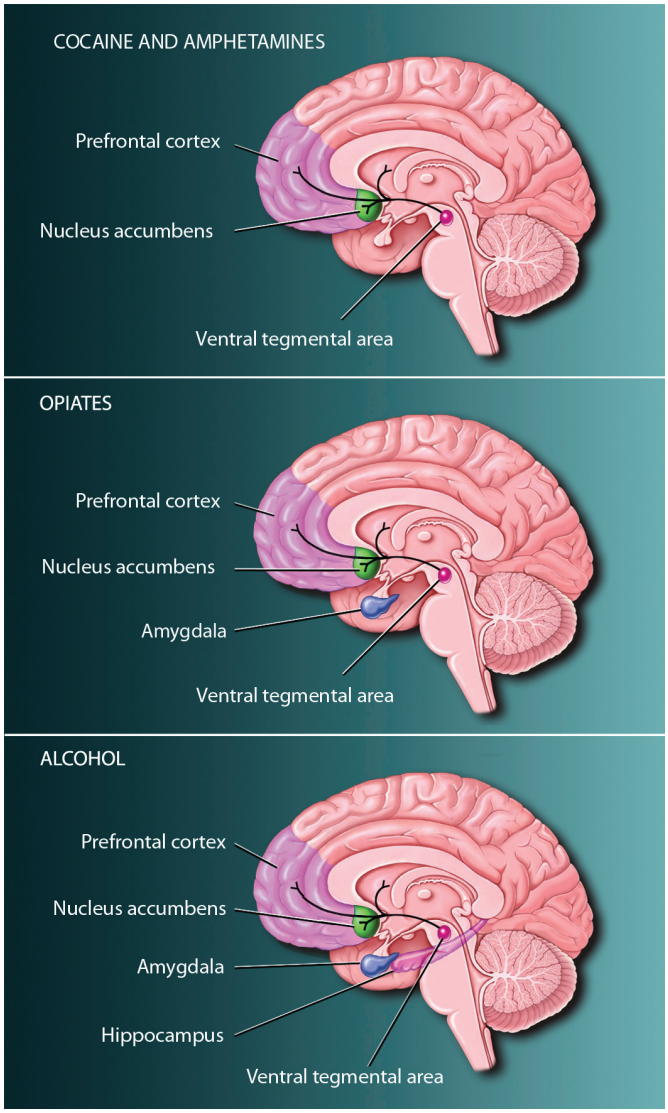
Although legal, alcohol is addictive. Together, alcohol abuse and alcohol addiction — sometimes referred to as alcoholism or alcohol dependence — are among the nation's major health problems. It is clear that genetic and environmental factors contribute to alcoholism, but at this point, no single factor or combination of factors enables doctors to predict who will develop an addiction to alcohol. Nearly17.6 million people abuse alcohol or are alcoholic. Fetal alcohol syndrome, affecting about 1 to 3 of every 1,000 babies born in the United States, is the leading preventable cause of mental retardation. Cirrhosis, or scarring of the liver, is the main chronic health problem associated with alcohol addiction. Other chronic liver diseases are responsible for more than 29,000 deaths each year. The annual cost of alcohol abuse and addiction is estimated at $185 billion.

Ethanol, the active ingredient in alcoholic beverages, is a seductive drug. At first, it reduces anxiety, tension, and behavioral inhibitions. In low doses, it may act as a stimulant, but at higher doses, it acts as a depressant. In both cases, it significantly alters mood and behavior. Too much alcohol can also cause heat loss and dehydration.

The drug, which is easily absorbed into the bloodstream and the brain, affects several neurotransmitter systems. For example, alcohol's interaction with the gamma-aminobutyric acid (GABA) receptor can calm anxiety, impair muscle control, and delay reaction time. At higher doses, alcohol also decreases the function of N-methyl-d-aspartate (NMDA) receptors, which recognize the neurotransmitter glutamate. This interaction can cloud thinking and eventually lead to coma.

In addition, animal research has shown that alcohol works by activating the endogenous opioid system. This means that susceptible individuals may feel an opioid-like euphoria from their own endorphins when they drink. Earlier, a medication called naltrexone had been developed for heroin addiction, which also affects the opioid system.

Naltrexone works by blocking opioid receptors. Researchers thought that this medication might be effective for alcoholics as well. Clinical trials began in 1983, and in 1995, the U.S. Food and Drug Administration (FDA) approved naltrexone for the treatment of alcoholism.




A central group of structures is common to the actions of all drugs. These structures include a collection of dopamine-containing neurons found in the ventral tegmental area. These neurons are connected to the nucleus accumbens and other areas, such as the prefrontal cortex. Cocaine is one drug that exerts its effects mainly through this system. Opiates also act in this system and many other brain regions, including the amygdala. Alcohol activates the core reward system and additional structures throughout the brain because it acts where GABA and glutamate are used as neurotransmitters.

## Marijuana

This drug distorts perception and alters the sense of time, space, and self. In certain situations, marijuana can produce intense anxiety. Researchers have made some progress in uncovering the reasons for these responses.

In radioactive tracing studies, scientists found that tetrahydrocannabinol (THC), the active ingredient in marijuana, binds to specific receptors called cannabinoid receptors, many of which coordinate movement. This may explain why people who drive after they smoke marijuana are impaired. The hippocampus, a structure involved with memory storage and learning, also contains many receptors for THC. This finding provides some insight into why heavy users or those intoxicated on marijuana have poor short-term memory and problems processing complex information.

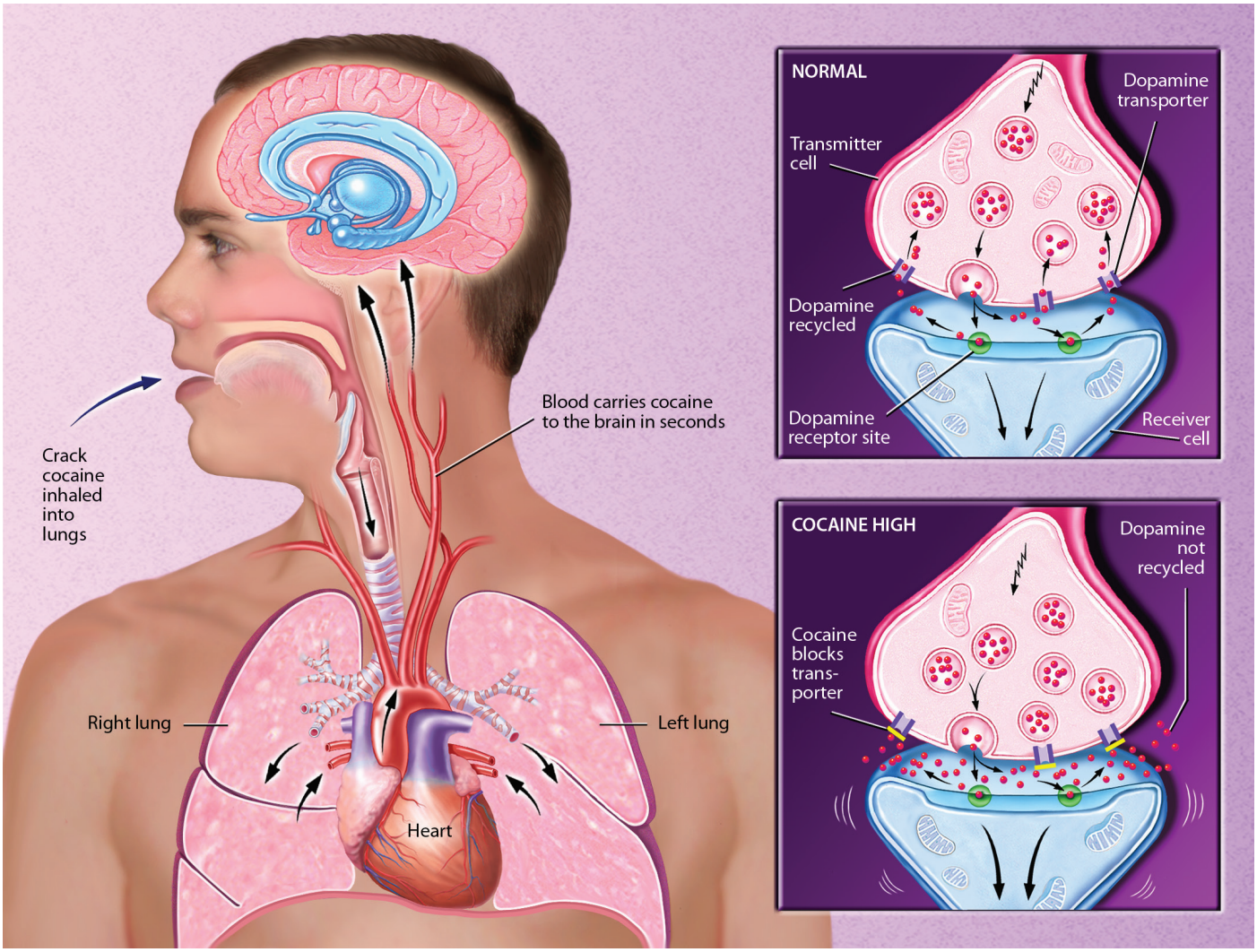
Scientists recently discovered that cannabinoid receptors normally bind to natural internal chemicals termed endocannabinoids, one of which is called anandamide. A large effort is now being made to develop medications that target the endogenous, or internal, cannabinoid system. The hope is that these medications will prove beneficial in treating a number of different brain disorders, including addiction, anxiety, and depression.

## Opiates

Humans have used opiate drugs, such as morphine, for thousands of years. Monkeys and rats readily self-administer heroin or morphine and, like humans, will become tolerant and physically dependent with unlimited access. Withdrawal symptoms range from mild, flulike discomfort to severe muscle pain, stomach cramps, diarrhea, and unpleasant mood.

Opiates increase the amount of dopamine released in the brain reward system and mimic the effects of endogenous opioids. Heroin injected into a vein reaches the brain in 15 to 20 seconds and binds to opiate receptors found in many brain regions, including the reward system. Activation of the receptors in the reward circuits causes a brief rush of intense euphoria, followed by a couple of hours of a relaxed, contented state.

Opiates create effects like those elicited by the naturally occurring opioid peptides. They relieve pain, depress breathing, cause nausea and vomiting, and stop diarrhea — important medical uses. But in large doses, heroin can make breathing shallow or stop it altogether — the cause of death




Crack cocaine enters the bloodstream through the lungs. Within seconds, it is carried by the blood to the brain. The basis for increased pleasure occurs at the synapse. Dopamine-containing neurons normally relay their signals by releasing dopamine into many synapses. Dopamine crosses the synapse and fits into receptors on the surface of the receiving cell. This triggers an electrical signal that is relayed through the receiver. Then, to end the signal, dopamine molecules break away from the receptors and are pumped back into the nerve terminals that released them. Cocaine molecules block the pump, or transporter, causing more dopamine to accumulate in the synapse. Pleasure circuits are stimulated again and again, producing a sense of euphoria.

in thousands of people who have died of heroin overdose.

A standard treatment for opiate addiction involves methadone, a long-acting oral opioid that helps keep craving, withdrawal, and relapse under control. Methadone helps opiate addicts rehabilitate themselves by preventing withdrawal symptoms that can motivate continued drug use. Naloxone and naltrexone are available medications that act as antagonists at opioid receptors; that is, they can curb the allure of opiates by blocking the opiate receptors so that opiates produce no pleasurable effects when they are taken. The blockers alone are sometimes useful for addicts who are highly motivated to quit. In addition, scientists are developing a long-lasting version of naltrexone that needs to be taken only once a month.

Another medication used to treat heroin addiction, buprenorphine, causes a weaker effect on the receptors than methadone and creates only a limited high, which deters an addict from abusing the medication itself. Buprenorphine has been prescribed for more than 500,000 patients in the United States.

## Psychostimulants

This class of drugs includes cocaine and amphetamines. In 2009, in the United States, an estimated 4.8 million people age 12 and older had abused cocaine. A popular, chemically altered form of cocaine, crack, is smoked. It enters the brain in seconds, producing a rush of euphoria and feelings of power and self-confidence. A form of methamphetamine that can be smoked, "crystal meth," also has become popular. The key biochemical factor underlying the reinforcing effects of psychostimulant drugs is their ability to greatly elevate the brain chemical dopamine in specific brain regions, such as the nucleus accumbens. Alterations in dopamine activity in the accumbens, induced by chronic cocaine intake, are thought to result in a progressively increasing motivation to take the drugs, eventually leading to addiction.

Cocaine users often go on binges, consuming a large amount of the drug in just a few days. A crash occurs after this period of intense drug-taking, resulting in such symptoms as emotional and physical exhaustion and depression. These symptoms may come from an actual shutdown, or crash, in dopamine and serotonin function, as well as an increased response of the brain systems that react to stress. Vaccines to produce antibodies to cocaine in the bloodstream are in clinical trials.

## Club Drugs

Ecstasy, herbal ecstasy, rohypnol ("roofies"), GHB (gamma hydroxy-butyrate), and ketamine are among the drugs used by some teens and young adults as part of raves and trances. These drugs are rumored to increase stamina and to produce intoxicating highs that are said to deepen the rave or trance experience. Recent research, however, is uncovering the serious damage that can occur in several parts of the brain from use of some of these drugs.

MDMA, called "adam," "ecstasy," or "XTC" on the street, is a synthetic psychoactive drug with hallucinogenic and amphetamine-like properties. Users encounter problems similar to those found with the use of amphetamines and cocaine. Recent research also links chronic ecstasy use to long-term changes in those parts of the brain critical for thought, memory, and pleasure.

Rohypnol, GHB, and ketamine are predominantly central nervous system depressants. Because they are often colorless, tasteless, and odorless, they can be added easily to beverages and unknowingly ingested. These drugs have emerged as the so-called date-rape drugs. When mixed with alcohol, rohypnol can incapacitate victims and prevent them from resisting sexual assault. Rohypnol may be lethal when mixed with alcohol and other depressants.

*If continued long enough, drug abuse can eventually alter the very structure and chemical makeup of the brain.*

Since about 1990 in the United States, GHB has been abused for its euphoric, sedative, and anabolic (body-building) effects. It, too, has been associated with sexual assault. Ketamine is another central nervous system depressant abused as a date-rape drug. Ketamine, or "Special K," is a fast-acting general anesthetic. It has sedative, hypnotic, analgesic, and hallucinogenic properties. It is marketed in the United States and a number of foreign countries as a general anesthetic — a drug that brings about a reversible loss of consciousness — in both human and veterinary medical practice.

Many users tend to experiment with a variety of club drugs in combination. This practice creates a larger problem, because combinations of any of these drugs, particularly with alcohol, can lead to unexpected adverse reactions and even death after high doses. Physical exhaustion also can enhance some toxicities and problems.

# Chapter 12: Degenerative Disorders

## In this Chapter



## Alzheimer's Disease

One of the most frightening and devastating of all neurological disorders is the dementia that can occur in the elderly. The most common form of this illness is Alzheimer's disease. Rare before age 60 but increasingly prevalent in each decade thereafter, Alzheimer's affects 5 percent of Americans age 65 to 74 and nearly half of those age 85 and older. As many as 5.3 million Americans have Alzheimer's. The disease is predicted to affect approximately 14 million individuals in the United States by the year 2050.

The earliest symptoms of Alzheimer's include forgetfulness; disorientation as to time or place; and difficulty with concentration, calculation, language, and judgment. As the disease progresses, some patients have severe behavioral disturbances and may even become psychotic. In the final stages, the affected individual is incapable of self-care and becomes bedridden. Patients usually die from pneumonia or some other complication of immobility. Alzheimer's disease is the seventh leading cause of death in the United States and the fifth leading cause of death for Americans aged 65 and older.

In the earliest stages, the clinical diagnosis of possible or probable Alzheimer's can be made with greater than 80 percent accuracy. As the course of the disease progresses, the accuracy of diagnosis at Alzheimer's research centers exceeds 90 percent. The diagnosis depends on medical history, physical and neurological examinations, psychological testing, laboratory tests, and brain imaging studies. New brain imaging strategies promise to enable doctors to visualize Alzheimer's neuropathology during life. At present, however, final confirmation of the diagnosis requires examination of brain tissue, usually obtained at autopsy.

The causes and mechanisms of the brain abnormalities underlying Alzheimer's are not yet fully understood, but great progress has been made through the study of genetics, biochemistry, and cell biology, as well as the use of experimental treatments. Neuroscientists do know that reductions occur in markers for many neurotransmitters that allow cells to communicate with one another. These include acetylcholine, somatostatin, monoamines, and glutamate. Damage to these neural systems, which are critical for attention, memory, learning, and higher cognitive abilities, is believed to cause the clinical symptoms.

Microscopic examination of brain tissue from people who died from Alzheimer's shows abnormal accumulations of a small fibrillar peptide, termed beta amyloid, in the spaces around synapses. These accumulations of tissue are referred to as neuritic plaques. Another abnormal clump of proteins, called neurofibrillary tangles, have been identified as a modified form of the protein tau, which is found in the cell bodies of neurons. In all forms of Alzheimer's, plaques and tangles mostly develop in brain regions important for memory and intellectual functions. New brain imaging strategies that may one day be used for diagnosis use a mildly radioactive chemical marker that shows amyloid plaques and tau tangles in living people.

Early-onset Alzheimer's disease is a rare, dominantly inherited form of the disease. Recently, scientists have identified Alzheimer's disease-associated mutations. The gene encoding the amyloid precursor protein (APP) is on chromosome 21. In some families with early-onset Alzheimer's, mutations have been identified in the presenilin 1 and 2 genes. Genes that cause dominant Alzheimer's appear to do so by causing beta amyloid plaques to accumulate. Apolipoprotein E (apoE), which influences

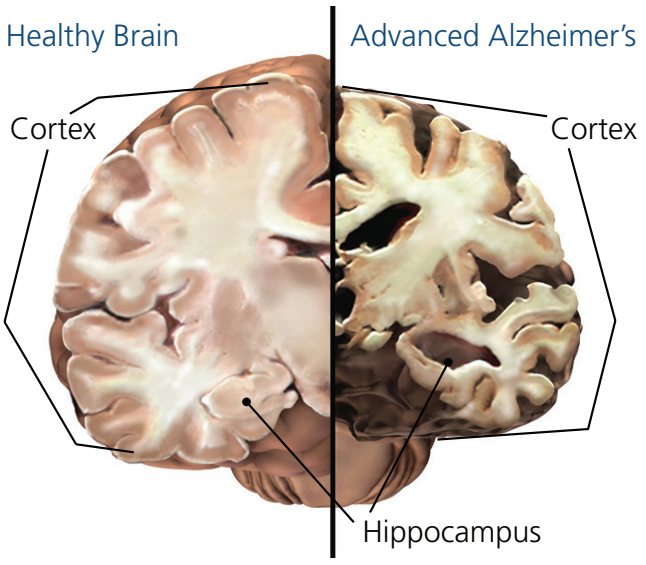
susceptibility for Alzheimer's later in life, exists in three forms. The variant known as APOE epsilon 4 is clearly associated with enhanced risk.

**Latest Research and Treatments** Currently approved treatments for Alzheimer's disease do not modify the course of the disease and offer only temporary mitigation of some symptoms, such as agitation, anxiety, unpredictable behavior, sleep disturbances, and depression. Five drugs have been approved by the FDA to treat Alzheimer's. Four prevent the breakdown of acetylcholine, a brain chemical important for memory and thinking. The fifth regulates glutamate, a brain chemical that may cause brain cell death when produced in large amounts. These agents temporarily improve memory deficits and provide some symptomatic relief but do not prevent progression of the disease. Several other approaches, such as antioxidants, are being tested.

An exciting area of research is the introduction of Alzheimer's disease-causing genes in mice. These mice, carrying mutant genes linked to inherited Alzheimer's, develop behavioral abnormalities and some of the microscopic changes in tissue structure that occur in humans. It is hoped that these mouse models will prove useful for studying the mechanisms of the disease and testing novel therapies, although appropriate caution must be taken. Experimental therapies in models of other neurodegenerative diseases — amyotrophic lateral sclerosis, for example — have been effective in mice with the disease but not in humans.

Researchers have begun to modulate the actions of genes that play critical roles in the production of amyloid in animal models. These genes encode beta and gamma secretases, which cut amyloid peptide from a larger protein. The amyloid peptide is then released from the neuron into the space around synapses, where it can accumulate and form Alzheimer's disease plaques. Amyloid-destroying enzymes, known as alpha secretases, break up the amyloid peptide, preventing amyloid accumulation. Anti-amyloid therapies for Alzheimer's aim either to remove existing amyloid or decrease production of new amyloid.

Within the past three to five years, greater appreciation has developed for the surprisingly important roles that diet and lifestyle play in determining risk for Alzheimer's disease. Cognitive activity, physical activity, and heart-healthy diets lower the risk for Alzheimer's, while obesity, high blood pressure, high cholesterol, metabolic syndrome, and diabetes raise the risk. Some evidence indicates that successful management of these cardiovascular risks can delay the onset or slow the progression of dementia.




Alzheimer's disease primarily affects the hippocampus and cortex regions of the brain, probably by damaging and destroying the connections between brain cells and later by causing cell death. Although initial symptoms are minor, this damage leads to impairments in learning, memory, and thinking and is eventually fatal. [Credit: Adapted and reprinted with permission from the Alzheimer's Association. © 2008 Alzheimer's Association.]

## Amyotrophic Lateral Sclerosis (ALS)

This progressive disorder strikes approximately 5,600 Americans annually, with an average survival time of just two to five years from symptom onset. It is the most common disorder within a group of diseases affecting motor neurons. Typically, 30,000 Americans have the disease at any given time. The costs of both care and treatment for ALS are expensive, and they continue to rise as the disease progresses. In the final stages, ALS can cost as much as $200,000 a year per family, and costs Americans some $300 million annually.

Commonly known as Lou Gehrig's disease, ALS affects neurons that control voluntary muscle movements such as walking. For reasons that are not completely understood, motor neurons in the brain and spinal cord begin to disintegrate. Because signals from the brain are not carried by these damaged nerves to the body, the muscles begin to weaken and deteriorate from the lack of stimulation and resulting disuse.

The first signs of progressive paralysis are usually seen in the hands and feet or in the muscles of speech and swallowing. Early symptoms include weakness in the legs, difficulty walking, clumsiness of the hands when washing and dressing, and slurred speech. Eventually, almost all muscles under voluntary control, including those of the respiratory system, are affected. Despite the paralysis, however, the mind and the senses remain intact. Death is usually caused by respiratory failure or pneumonia.

No specific test identifies ALS, but electrical tests of muscle activity, muscle biopsies, blood studies, computed tomography (CT), and magnetic resonance imaging (MRI) scans help diagnose the disease and rule out other disorders.

In more than 90 percent of cases, ALS is sporadic, arising in individuals with no known family history of the disorder. Potential causes or contributors to the disease include an excess amount of the neurotransmitter glutamate, which becomes toxic; oxygen in a dangerous form in the body, resulting in what is called oxidative distress; environmental factors; and an autoimmune response in which the body's defenses turn against body tissue. In the other 5 to 10 percent of cases, ALS is familial — transmitted to family members because of a gene defect.

Scientists have now identified several genes that are responsible for some forms of ALS. The most common and well-studied of these are mutations in the gene that codes for superoxide dismutase, a defense against oxidative distress. Scientists believe that whatever they learn from studying this and other genes will have relevance for understanding the more common, sporadic form of this motor neuron disease.

Once ALS is diagnosed, there is little that can be done to slow its progression. Various drugs can ease specific problems, such as muscle cramping and neurological stiffness, but there is no cure. An anti-glutamate drug slows the disease's progression modestly. Additional drugs are now under study. Protecting or regenerating motor neurons using nerve growth factors, other more potent drugs, and stem cells may someday provide additional benefits for patients.

## Huntington's Disease

Affecting some 30,000 Americans and placing 200,000 more Americans at risk for inheriting the disease from an affected parent, Huntington's disease is now considered one of the most common hereditary brain disorders. The disease progresses slowly over a 10- to 20-year period and eventually robs the affected individual of the ability to walk, talk, think, and reason. Huntington's disease usually appears between the ages of 30 and 50. It affects both the basal ganglia, which controls coordination, and the brain cortex, which serves as the center for thought, perception, and memory.

*Affecting some 30,000 Americans and placing 200,000 more at risk, Huntington's disease is now considered one of the most common hereditary brain disorders.*

The most recognizable symptoms include involuntary jerking movements of the limbs, torso, and facial muscles. These are often accompanied by mood swings, depression, irritability, slurred speech, and clumsiness. As the disease progresses, common symptoms include difficulty swallowing, unsteady gait, loss of balance, impaired reasoning, and memory problems. Eventually, the individual becomes totally dependent on others for care, with death often due to pneumonia, heart failure, or another complication.

Diagnosis consists of a detailed clinical examination and family history. Brain scans may be helpful. The identification in 1993 of the gene that causes Huntington's has simplified genetic testing, which can be used to help confirm a diagnosis. Researchers and genetic counselors, however, have established specific protocols for predictive genetic testing to ensure that the psychological and social consequences of a positive or negative result are understood. Predictive testing is available only for adults, though children under the age of 18 may be tested to confirm a diagnosis of juvenile-onset Huntington's disease. Prenatal testing may be performed. The ethical issues of testing must be considered, and the individual must be adequately informed, because there is no effective treatment or cure, although medications are available to help control some of the symptoms.

The Huntington's disease mutation is an expanded triplet repeat — a kind of molecular stutter in the DNA. This abnormal gene codes for an abnormal version of the protein called huntingtin. The huntingtin protein, whose normal function is still unknown, is widely distributed in the

brain and appears to be associated with proteins involved in transcription (turning genes on), protein turnover, and energy production. Scientists suspect that Huntington's disease is caused by the gain of a new and toxic function among these proteins.

Cell and animal models can replicate many features of the disease and are now being used to test new theories and therapies. Although no effective treatments for slowing disease progression currently exist, clinical and observational trials are being conducted. Any of these may yield an effective treatment that would slow the progression or delay onset of the disease while researchers continue working toward a cure.

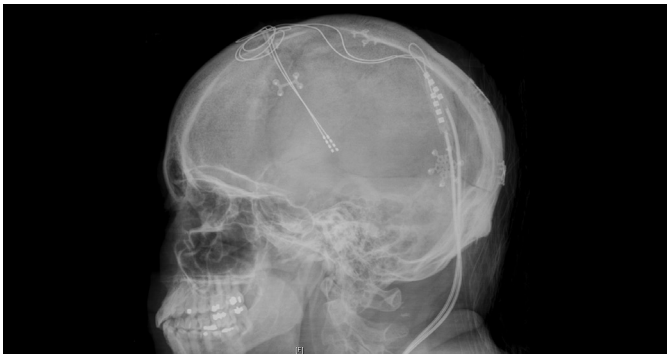
## Parkinson's Disease

Parkinson's disease is a progressive neurological disorder that affects approximately 1.5 million individuals in the United States. Typically, people start showing symptoms over the age of 50. In fact, aging is the only known risk factor for the development of this disorder.

Parkinson's disease is characterized by slowness of movement, muscular rigidity, and walking and balance impairment. Many affected individuals may develop a resting tremor as well. Besides impairment in motor movement, Parkinson's may also cause changes in non-motor brain function.

On a cellular level, Parkinson's disease is the result of the loss of dopamine-producing cells in the region of the brain called the substantia nigra pars compacta, found in the midbrain. A large number, 40 percent, of cells must be lost before symptoms occur, suggesting that perhaps the brain has a way of warding off symptoms. Eventually, however, these mechanisms begin to fail, or the continued loss of cells leads to a threshold from which the brain can no longer recover.

Although the cause of Parkinson's remains unknown, most researchers believe that there are both genetic and environmental factors that contribute to the injury and eventual loss of these dopamine-producing cells. While most cases of Parkinson's do not appear to be inherited, there are certain situations in which genetic factors may be involved. For example, studies indicate that cases of early onset Parkinson's may be inherited. Research on various forms of the disease may help provide clues about it, as well as insights into potential new treatments.



Deep brain stimulation shows promise at relieving symptoms for some people with Parkinson's disease. As shown in the X-ray image, the therapy uses an implanted electrode to deliver electrical impulses deep within the brain. [Credit: Courtesy of Robert S. Fisher, MD, PhD, Stanford Neurology and Jaimie Henderson, MD, PhD, Stanford Neurosurgery.]

### Treatment Breakthroughs — and the Need for More Research

The discovery in the late 1950s that the level of dopamine was decreased in the brains of Parkinson's patients was followed in the 1960s by successful treatment with the drug levodopa, which is converted to dopamine in the brain. This historical event is one of the greatest medical breakthroughs in the field of neurology.

Since the discovery of levodopa, other drugs have been developed to either boost the effect of dopamine, by inhibiting its breakdown, or extend the length of dopamine-like effects, through their ability to bind and act on similar brain regions for longer periods of time. For example, a drug called carbidopa is often combined with levodopa; the combination is effective in that it reduces the breakdown of levodopa in the bloodstream, allowing greater levels of dopamine to reach the brain. It also reduces side effects, such as nausea.

Although dopamine replacement therapy is very effective in alleviating many of the motor symptoms of Parkinson's, there still remains a critical need to find better treatments. For one thing, dopamine replacement therapy neither cures the disease nor slows its progression. In addition, dopamine replacement is not optimal for treating non-motor aspects of the disease, such as anxiety and sleep issues. What's more, this treatment becomes less effective over time in helping with gait and balance problems.

Because many unanswered questions remain in our understanding of Parkinson's, more medical research is greatly needed. Using animal models is an effective way to learn more about the disease and to

identify new and better treatments and potential cures. Rodent and nonhuman primate models are among the many valuable animal models used to investigate important, specific questions about the disorder.

One common rodent and nonhuman primate model uses the neurotoxin MPTP (1-methyl-4-phenyl-1, 2, 3, 6 tetrahydropyridine). MPTP was first discovered in the late 1970s, when it was accidentally synthesized by designers of illicit drugs looking for ways to produce a heroin-like compound. The drug addicts who self-injected the MPTP-contaminated preparations developed a neurological condition that was indistinguishable from Parkinson's. Researchers soon found that MPTP is converted in the brain to a substance that destroys dopamine neurons. This finding led to using MPTP as a tool for medical studies.

Over the past several decades, scientists have shown that in primate models of Parkinson's, there are specific regions in the basal ganglia, the group of cellular structures deep in the brain, that are abnormally overactive. Most important, they found that surgical deactivation or destruction of these overactive structures — the pallidum and subthalamic nucleus — can greatly reduce symptoms of Parkinson's disease.

*Neuroscience research focusing on Parkinson's disease is moving forward by exploring many avenues simultaneously.*

The past decade has witnessed a resurgence in this surgical procedure, called pallidotomy. More recently, chronic deep-brain stimulation has been used. These techniques are highly successful for treating patients who have experienced significant worsening of symptoms and are troubled by the development of drug-related involuntary movements.

Also on the horizon are attempts to treat Parkinson's patients whose disease is progressing rapidly with surgical implantation of cells, such as fetal cells, capable of producing dopamine. Replacement therapy with stem cells is being explored as well. In addition, gene transfer of trophic factors has been studied in animal models and is being tested in clinical trials. Clinical trials also are testing the hypothesis that gene therapy can provide symptomatic or neuroprotective benefit to patients with Parkinson's. While there is clearly much work to do, neuroscience research focusing on Parkinson's is moving forward by exploring many avenues simultaneously. The hope is to find better treatments — and eventually, perhaps, a cure.

# Chapter 13: Psychiatric Disorders

## In this Chapter



## Anxiety Disorders

Considered the most common mental illnesses, anxiety disorders affect an estimated 18 percent of the adult population in a given year, or 40 million Americans. Anxiety disorders include obsessive-compulsive disorder (OCD); panic disorder; phobias, such as acrophobia, or fear of heights and; agoraphobia, or fear of open spaces; social anxiety disorder; generalized anxiety disorder; and post-traumatic stress disorder (PTSD). These disorders can be crippling, to the point of keeping people completely housebound. What's more, anxiety disorders often occur with depression, and individuals doubly afflicted are at a high risk of suicide.

Discussed below are a few of the more prevalent anxiety disorders. These summaries provide a snapshot of the nature of anxiety disorders, how they are studied, and the treatments that are currently being used.

**OCD** People with OCD become trapped, often for many years, in repetitive thoughts and behaviors, which they recognize as groundless but cannot stop. Such behavior includes repeatedly washing hands or checking that doors are locked or stoves turned off. The illness is estimated to affect 2.2 million American adults annually. One-third of adults develop their symptoms as children.

Neuroscientists think that environmental factors and genetics probably play a role in the development of the disorder. Positron emission tomography (PET) scans reveal abnormalities in both cortical and deep areas of the brain, implicating central nervous system changes in individuals with OCD.

OCD is not limited to people either. Scientists have recently discovered that certain breeds of large dogs develop acral lick syndrome, severely sore paws from compulsive licking. These dogs respond to the serotonergic antidepressant clomipramine, which was the first effective treatment developed for people with OCD. This and other serotonergic antidepressants, as well as selective serotonin *reuptake* inhibitors (SSRIs) such as sertraline and paroxetine, are effective in treating OCD. A specialized type of behavioral intervention, called exposure and response prevention, also is effective in many patients.

**Panic Disorder and Phobias** With a lifetime prevalence rate of 4.7 percent in the United States, panic disorder usually starts unexpectedly. Patients experience an overwhelming sense of impending doom, accompanied by sweating, weakness, dizziness, and shortness of breath. With repeated attacks, patients may develop anxiety in anticipation of another attack. As a result, people may avoid public settings where attacks might occur. If these individuals are untreated, they may develop agoraphobia and become virtually housebound. Antidepressants, including SSRIs, are effective, as is cognitive behavioral therapy.

Phobia is an intense, irrational fear of a particular object or situation. Individuals can develop phobias of almost anything, including dogs, dating, blood, snakes, spiders, or driving over bridges. Exposure to the feared object or situation can trigger an extreme fear reaction that may include a pounding heart, shortness of breath, and sweating. Cognitive behavioral therapy is an effective treatment. It is likely that panic disorders and phobias have similar neurochemical underpinnings that emerge as the result of a particular "stressor."

**Post-Traumatic Stress Disorder** Extreme stressors such as trauma in combat, being a victim of assault or sexual abuse, or experiencing or witnessing a crime can lead to a form of stress that can last a lifetime. In the United States, this

condition, called post-traumatic stress disorder, or PTSD, has a lifetime prevalence rate of 6.8 percent (9.7 percent in women and 1.8 percent in men). It is characterized by intense fear, helplessness or horror, intrusive recollections of the traumatic event, avoidance and numbing, and hyperarousal. In addition, PTSD is associated with dysregulation of stress hormones, disordered sleep, and major depressive disorder. Military personnel are at elevated risk for exposure to trauma, so not surprisingly, they have higher prevalence rates compared to the general population.

Scientists have studied PTSD in depth and have learned that the very high levels of norepinephrine released in the brain during stress remain at heightened levels. Medications that work well for patients with PTSD have emerged from basic research into norepinephrine's actions in different brain regions. The alpha-1 blocker prazosin, a drug used to lower blood pressure for more than 20 years, is now used to treat nightmares experienced with PTSD. People treated with prazosin include those with a very long-standing illness, such as Holocaust survivors. Beta-blockers such as propranolol also are being tested in individuals exposed to trauma, but these agents must be administered shortly after the trauma, before PTSD has been established, which brings up complex ethical issues. PTSD also is treated with antidepressant and atypical antipsychotic medications and psychotherapies, such as cognitive behavioral therapy or eye movement desensitization and reprocessing therapy.

The discovery of brain receptors for the benzodiazepine antianxiety drugs has sparked research to identify the brain's own antianxiety chemical messengers. Benzodiazepines bind to GABA receptors and enhance responsiveness to endogenous GABA, the major inhibitory neurotransmitter in the brain. Indeed, recent studies have revealed alterations in certain GABA receptors in the central nervous system of patients with PTSD, effectively providing an additional neurochemical link between different anxiety disorders. This finding may lead to new ways to modulate anxiety disorders.

## Tourette Syndrome

One of the most common and least understood neurobiological disorders, Tourette syndrome is an inherited disorder that affects about 200,000 Americans. Males are affected three to four times as often as females.

Symptoms usually appear between the ages of four and eight, but in rare cases may emerge in the late teenage years. The symptoms include motor and vocal tics — repetitive, involuntary movements or utterances that are rapid, sudden and persist for more than one year. The types of tics may change frequently and increase or decrease in severity over time. In roughly one-half of individuals, this disorder lasts a lifetime, but the remaining patients may experience a remission or decrease in symptoms as they get older. A high percentage of people with Tourette syndrome also have associated conditions, such as problems with learning, difficulties with attention, obsessive thoughts and compulsive rituals. Often these manifestations are more troublesome to individuals than the tics themselves, so physicians must consider them when choosing a treatment regimen.

Tourette syndrome is inherited and seems to result from abnormal activity in a brain system called the basal ganglia. Research suggests that genes associated with Tourette's, perhaps together with in utero or early environmental conditions, cause abnormalities in basal ganglia development or excesses in certain chemicals, including the neurotransmitter dopamine.

The majority of people with Tourette syndrome are not significantly disabled by symptoms, so they do not require medication. However, antipsychotics and SSRIs, as well as drugs to control tics, nausea, high blood pressure, seizures, or anxiety, are available to help control symptoms when they interfere with functioning. Stimulant medications such as methylphenidate and dextroamphetamine, which are prescribed for attention deficit hyperactivity disorder (ADHD), have been reported to improve attention and decrease tics in Tourette syndrome. For obsessive-compulsive symptoms that interfere significantly with daily functioning, SSRIs, antidepressants, and related medications may be prescribed.

Medication dosages that achieve maximum control of symptoms vary for each person and must be gauged carefully by a doctor. The medicine is administered in small doses, with gradual increases to the point where there is maximum alleviation of symptoms with minimal side effects. Some of the undesirable reactions to medications are weight gain, muscular rigidity, fatigue, motor restlessness, and social withdrawal. Most of these side effects can be reduced with specific medications. Other side effects, such as depression and cognitive impairment, can be alleviated with dosage reduction or a change of medication.

Other types of therapy also are helpful. Behavioral therapies, such as those used to treat similar disorders that emerge in childhood, have been receiving more attention. Aimed at training circuits to control the specific behavior related to the tic, these therapies have proven to be highly

effective in reducing the severity of tics in some subtypes of Tourette syndrome. Psychotherapy and counseling can assist people with this disorder, as well as providing coping mechanisms for family members.

## Major Depression

Clinical or major depression, with its harrowing feelings of sadness, hopelessness, pessimism, loss of interest in life, and reduced emotional well-being, is one of the most common and debilitating mental disorders. The disorder also comes with disturbances of sleep and appetite, decreased energy, and often cognitive disturbances such as difficulty concentrating and remembering. Depression is as disabling as heart disease or arthritis. What's more, depressed individuals are at a significantly elevated risk of suicide.

While both genes and the environment play a role in an individual's risk for depression, stress also can trigger a depressive episode. We now know that the physical symptoms may reflect disturbances in the hypothalamus, resulting in an excessive production of stress hormones. This has been shown in the laboratory: Many depressed patients fail to shut off secretion of the stress hormone cortisol in response to potent synthetic analogs that normally feed back to shut off secretion. Experiments with positron emission tomography (PET) imaging have also implicated a region of the anterior cingulate gyrus within the prefrontal cerebral cortex in depression. This region, which normally integrates aspects of cognition and emotion, is the chief experimental target for deep brain stimulation in severely depressed patients who have not responded to other treatments.

In the United States, the lifetime risk of a depressive episode severe enough to warrant treatment is approximately 18 percent. Put another way, in the past 12 months, 6.7 percent of U.S. adults experienced a major depression. Fortunately, 80 percent of these individuals respond to drugs, psychotherapy, or a combination of the two. Some severely depressed patients can be helped with electroconvulsive therapy. As mentioned above, those patients who do not respond to the standard antidepressant drugs may be helped by deep brain stimulation approaches, which were originally developed for patients with neurodegenerative disease.

Currently, approved antidepressant drugs increase levels of norepinephrine or serotonin in synapses. A few medications also target dopamine. The well-known selective serotonin reuptake inhibitors, or SSRIs, act on serotonin alone. The increased levels of neurotransmitters then initiate plastic changes in cells and circuits, leading to an improvement in symptoms over several weeks. In addition, cognitive behavioral psychotherapies have been shown to be effective.

Recently, ketamine, a drug that blocks NMDA glutamate receptors, has been shown to alleviate depressed symptoms rapidly. Because ketamine has many side effects, it is not likely to be used clinically, but these findings have set off an exciting search for new pharmacologic approaches.

*Depression is as disabling as heart disease or arthritis.*

## Bipolar Disorder

People with bipolar disorder, previously known as manic-depressive illness, usually experience episodes of deep depression and manic highs. Many patients return to normal moods in between acute episodes, but a large number continue to have troubling symptoms, usually of depression. They also have an increased risk of suicide. The depressive episodes are indistinguishable from those of a major depression and are characterized by sad mood, loss of interest, lack of energy, disturbances of sleep and appetite, difficulty concentrating, feelings of hopelessness and worthlessness, suicidal thoughts, and sometimes suicidal acts.

Symptoms of mania include increased energy, decreased need for sleep, a marked interest in goal-directed activities, and poor judgment. For example, during manic episodes, individuals may spend excessively or engage in uncharacteristic drug abuse or sexual behaviors. Individuals with mania may be euphoric, but some are predominantly irritable. Typically, manic individuals are grandiose, and when the mania is particularly severe, they may have delusions or hallucinations. In such instances, patients may believe that they are prophets, deities, or on a special mission. Sometimes, too, mania can be mild. Then it is called hypomania.

Bipolar disorder that is characterized by full manic episodes and depressions affects about 1 percent of the population worldwide. When people who suffer from

hypomania along with depressions are factored in, the prevalence goes up to 2.6 percent. This finding is based on a study of Americans over the age of 18. In addition, about the same number of men and women suffer from bipolar disorder. People with this disorder typically have recurrences of acute mania or depression throughout their lives.

Bipolar disorder is highly influenced by genes. In fact, many different genes contribute to the risk of the disorder. Modern technology has allowed us to identify a small number of these genes. The study of the genetic basis of bipolar disorder continues to be a very active area of research.

Individuals with this disorder can benefit from a broad array of treatments. One of these is lithium. During the late 1940s, researchers showed that when guinea pigs were injected with lithium, they became placid, implying that the lithium had a mood-stabilizing effect. When given to manic patients, lithium improved all manic symptoms and stabilized their moods. This enabled people with the disorder to return to work and live relatively normal lives.

Although lithium is quite effective, many patients require additional treatments, especially for their depression. Other medications with mood-stabilizing effects used to treat bipolar disorder include some drugs, such as valproate, that were first developed as anticonvulsants. None of the existing drugs are perfect, and they all have side effects. As a result, additional research on bipolar disorder and its treatment continues to be an important priority.

## Schizophrenia

Marked by disturbances in thinking, cognition, emotional reactions, and social behavior, schizophrenia usually results in chronic illness and personality change. Delusions, hallucinations, and thought disorder are common, as are disturbances in attention, memory, and complex thinking. Affecting about 1.1 percent of the population, or 2.4 million Americans, schizophrenia is disabling and costly. Annual costs total about $62.7 billion.

Schizophrenia leads to changes that may be caused by the disruption of neurodevelopment through a genetic predisposition, which may be exacerbated by environmental factors such as maternal infections or direct brain trauma. Brain scans and postmortem studies show abnormalities in some people with schizophrenia, such as enlarged *ventricles* (fluid-filled spaces) and reduced size of certain brain regions. Functional neuroimaging scans such as PET and functional magnetic resonance imaging (fMRI) taken while individuals perform cognitive tasks, particularly those involving memory and attention, show abnormal functioning in specific brain areas of people with this illness. Brain systems using the chemicals dopamine, glutamate, and GABA appear to be particularly involved in the development of the disorder. Recently, mutations in several genes involved in controlling nerve cell communication have been identified that appear to increase the risk of developing schizophrenia.

The disorder usually is diagnosed between the ages of 15 and 25. Few patients recover fully following treatment, and most continue to have moderate or severe symptoms that may be aggravated by life stressors. About 15 percent of individuals return to a productive life after a single episode, 60 percent will have intermittent episodes throughout their lives, and an additional 25 percent will not recover their ability to live as independent adults. Deficits in cognition are frequent, lifelong manifestations in most patients, even those who show good recovery from more acute "positive" symptoms, such as hallucinations, delusions, and confused thinking. "Negative" symptoms, such as inability to experience pleasure and lack of motivation, may be the most debilitating part of the disorder. These symptoms make it difficult for many people to lead productive lives. Unfortunately, many of these symptoms are generally resistant to drug treatment.

The first antipsychotic drug, chlorpromazine, was discovered by accident in the 1950s and shown to reduce symptoms of schizophrenia. Clinical trials demonstrated that chlorpromazine was more effective than a placebo or a sedative. Subsequently, more than 20 effective antipsychotic drugs were developed. The first generation of antipsychotic drugs acts by inhibiting certain dopamine receptors. This mechanism accounts for the high prevalence of side effects, similar to those seen with Parkinson's, that are associated with the use of first-generation antipsychotics. The mechanism also explains the risk of developing an irreversible movement disorder, tardive dyskinesia, which results in aimless, uncontrollable movements, such as grimacing or rapid eye blinking.

The second generation of antipsychotic medications were developed to be more effective in treating the positive symptoms of schizophrenia. They do not have the same likelihood of causing Parkinsonian effects but can lead to other debilitating side effects, such as very large weight gain, blood disorders, and muscle pain and dysfunction. As a result of problems with both generations of antipsychotic medications, safer drugs with fewer side effects are currently being sought.

# Chapter 14: Injury and Illness

## In this Chapter



## Brain Tumors

Primary brain tumors develop within brain tissue. Such tumors can spread throughout the brain, but they are not always cancerous, or malignant. Malignant brain tumors can originate in the brain or spread to the brain from other parts of the body, a condition that becomes potentially lethal. The likelihood to grow faster and invade, coupled with the identification of specific cells within the tumor, are some of the criteria used to classify the tumor's severity, or grade. No matter what grade a brain tumor is assigned — and whether it's malignant or not — these growths are always serious because they can interfere with normal brain activity.

Brain tumors can be either primary or metastatic. Primary brain tumors arise within the brain, whereas metastatic (also called secondary) brain tumors spread from other parts of the body through the bloodstream and enter the brain. The incidence of primary brain tumors is about 19 cases per population of 100,000. About 35,000 new cases occur in the United States annually.

Symptoms of brain tumors vary according to the tumor's location and size, but seizures and headaches are among the most common. In particular, gliomas, typically malignant brain tumors, release the neurotransmitter glutamate at toxic concentrations. The glutamate kills off neurons near the tumor, making room for its expansion. The released glutamate is largely responsible for the seizures, which originate from tissue surrounding the tumor. An expanding tumor can increase pressure within the skull, causing headache, vomiting, visual disturbances, and impaired mental functioning. Brain tumors are diagnosed with MRI and CT scanning. Early imaging is beneficial because it can mean that tumors are identified at a lower grade, improving prognosis and outcome considerably.

Treatment options for primary brain tumors are limited. Surgery is generally the first step if the tumor is accessible and vital structures will not be disturbed. Radiation is used to stop a tumor's growth or cause it to shrink. Chemotherapy destroys tumor cells that may remain after surgery and radiation, but it is not very effective for gliomas, largely because it is hard for chemotherapeutic drugs to reach the brain. Steroid drugs relieve brain swelling and antiepileptic drugs control seizures.

New therapies for brain tumors are being developed in clinical trials. Many of these trials focus on targeted therapy — treatment aimed at the biologic characteristics of tumors. Targeted therapies include vaccines created from the patient's own tumor combined with substances that boost the immune system or kill tumor cells; monoclonal antibodies, which home in on receptors on the surface of the tumor cells; anti-angiogenic therapy, during which the tumor's blood supply is restricted; immunotherapy, which uses the body's own immune system against the tumor; gene therapy, which delivers bioengineered genes to the cancer cells to kill them; and several approaches for a targeted delivery of antibodies, toxins, or growth-inhibiting molecules that attach specifically to the tumor cells and interfere with their growth. A scorpion-derived toxin called chlorotoxin, which interferes with the spread of the tumor, has shown promise in clinical studies. This therapy extended life expectancy significantly.

Researchers are exploring the role of stem cells in the origin of brain tumors, and brain tumor research is being strongly influenced by the wealth of research into neural stem cells in particular. As the identification of the cellular components that make up different tumors becomes easier

(due to genomics technology and neural stem cell research), scientists will be able to better target the cells in the tumor that are most likely to be the most harmful. Epidemiologists, or scientists studying disease in human populations, also are looking into tumor genetics and patients' lifestyles, environments, occupations, and medical histories for clues about the causes of these tumors. International efforts are underway to increase awareness of brain tumors, encourage research collaboration, and explore new and innovative therapies.

## Multiple Sclerosis

*Multiple sclerosis* (MS) is a lifelong ailment of unknown origin that affects approximately 400,000 Americans and 2.5 million people worldwide. MS is diagnosed mainly in individuals between the ages of 20 and 40. The disease affects every aspect of a patient's life. In fact, in the United States, the disease results in earnings losses of about $10.6 billion annually for individuals with MS and their families.

MS is an autoimmune disease in which the body's natural defenses attack the myelin sheath covering the axons of neurons in the central nervous system. While neuroscientists do not know what causes this autoimmune assault, they have discovered that the loss of myelin results in damage to the nerve fibers. In some instances, the damage may be so severe that the nerve fiber deteriorates. The effects are comparable to the loss of insulating material around an electrical wire or cutting of the wire, which interferes with the transmission of signals. Following loss of myelin, the axon's sheath is either repaired or replaced by scars, or scleroses, of hardened patches of tissue. Scarring is usually associated with further degeneration of the nerve fibers. Areas of disease activity, called lesions or plaques, appear in multiple places within the central nervous system.

Siblings of people with MS are at a 2 to 3 percent risk of developing MS (10 to 15 times higher than the general population), whereas the risk for an identical twin of someone with MS is much higher — about 30 percent. In addition, the disease is as much as five times more prevalent in temperate zones, such as the northern United States and northern Europe, than it is in the tropics. Caucasians are more susceptible than other races. Thus, both genetic and environmental factors probably play a role in determining who contracts the disease. Previous studies had suggested that those who developed MS before the age of 15 were affected by environmental factors, but more recent, larger studies suggest that there is no exact age cutoff.

The symptoms of MS depend on the site of the damage. Because the spinal cord, cerebellum, and optic nerve are commonly affected, symptoms such as numbness, clumsiness, and blurred vision often occur. However MS can affect many other brain areas, including bundles of myelinated nerve fibers (white matter) and areas rich in neurons (gray matter), so symptoms may also include slurred speech, weakness, loss of coordination, pain, uncontrollable tremors, loss of bladder control, memory loss and other cognitive problems, depression, and fatigue. Symptoms due to an acute attack may last from several weeks to months and then spontaneously improve. This form of MS is known as relapsing/remitting. If, however, there is ongoing nerve fiber degeneration, symptoms become permanent and gradually worsen, causing progressive MS. This form of MS leads to a progressive accumulation of disability usually affecting mobility, strength, balance, and coordination.

At this point, MS cannot be cured, but several medications help control relapsing/remitting forms of MS by lixmiting the immune attack and reducing associated inflammation. Steroids, which have been used to treat MS for more than three decades, may be effective in shortening attacks, thus helping to speed recovery from MS-related acute attacks. What's more, an increasing range of newer, more selective drugs are now becoming available or are in clinical trials. While many medications and therapies are available to control symptoms such as muscle stiffness (spasticity), pain, fatigue, and mood swings, as well as bladder, bowel, or sexual dysfunction, no treatments are available for the nerve degeneration that causes the progression of the disease.

## Neurological AIDS

In 2009, about 2.5 million people worldwide became infected with human immunodeficiency virus (HIV); 33 million are now living with HIV. Advanced HIV infection is known as acquired immunodeficiency syndrome, or AIDS. The epidemic is still the most intense in sub-Saharan Africa, but it is gaining traction in Asia and Eastern Europe. The impact of AIDS in the United States has been tempered by more widespread use of life-prolonging drugs, making HIV a chronic illness instead of a death sentence. In developing countries, however, only about 36 percent of the people who need therapy are receiving such treatment. In addition, women now represent half of all cases worldwide.

Although the principal target of HIV is the immune system, the nervous system may be affected in varying

degrees. HIV-associated neurocognitive disorder (HAND) is a common complication affecting more than 50 percent of people with HIV. HAND also affects those receiving the modern combination antiretroviral treatment (CART), though not to the same degree. Individuals with HAND have mental problems ranging from mild difficulty with concentration, memory, complex decision-making or coordination to progressive, fatal dementia.

Despite advances in treating other aspects of the disease, HAND remains incompletely understood. Most current hypotheses center on an indirect effect of HIV infection related to secreted viral products or cell-coded signal molecules called cytokines. Some proteins of the virus itself are neurotoxic and may play a role in the ongoing damage that occurs during infection. Viral Tat, released by infected cells, has been among the proteins suspected of neurotoxicity. In any case, HIV infection appears to be the prime mover in this disorder because antiretroviral treatment may prevent or reverse this condition in many patients.

Milder forms of HAND have been reported in 30 to 40 percent of HIV-infected people who are medically asymptomatic. In advanced disease, patients can develop increasing difficulty with concentration and memory and experience general slowing of their mental processes. At the same time, patients may develop leg weakness and a loss of balance. Imaging techniques, such as CT and MRI, show that the brains of these patients have undergone some shrinkage. Examination of the brains of persons dying with AIDS can reveal loss of neurons, abnormalities in the white matter (tissue that serves to connect different brain regions), and injury to cellular structures that are involved in signaling between neurons. There also may be inflammation and vessel disease.

Recent studies indicate that highly active combination antiretroviral treatment — cocktails of three or more drugs active against HIV — is effective in reducing the incidence of severe HAND, termed AIDS dementia. Such treatment also can reverse, but not eliminate, the cognitive abnormalities attributed to brain HIV infection.

Peripheral neuropathy, a type of nerve injury in extremities that causes discomfort ranging from tingling and burning to severe pain, is also a major neurological problem commonly seen in HIV patients. It is believed that the virus triggers sensory neuropathy through neurotoxic mechanisms. This reaction has often been unmasked or exacerbated by certain antiretroviral drugs that produce *mitochondrial* toxicity, which tends to make the neuropathies more frequent and serious. More than half of patients with advanced disease have neuropathy, making it a major area for preventive and symptomatic therapeutic trials.

Despite remarkable advances in new therapies, some patients develop these neurological problems and fail to respond to treatment, thus requiring the development of additional ways to prevent and treat their symptoms. In addition, because of immunodeficiency in HIV patients, otherwise rare opportunistic infections and malignancies are seen more often in those with HIV. Fortunately, however, CART has greatly reduced the incidence of most of these kinds of infections.

## Neurological Trauma

Traumatic brain and spinal cord injuries can lead to significant disabilities and death. In the United States, an estimated 1.7 million people suffer traumatic head injuries each year, and roughly 52,000 will die. The leading causes of traumatic brain injury are falls and motor-vehicle related events.

Those who survive a brain injury face a lifetime of disability, with economic costs approaching $60 billion annually. An estimated 265,000 individuals in the United States are living with spinal cord injury. Each year, about 12,000 new injuries are reported, caused mostly by motor vehicle accidents, sports injuries, violence, and falls. The cost of caring for these individuals approaches $10 billion a year. Such facts point to the pressing need to advance our understanding of these injuries, with the goal of developing strategies to support long-term recovery.

No magic bullet has yet been found, but doctors have discovered methods to stave off severe neurological damage caused by head and spinal cord injuries and to improve neurological function. This is accomplished by working to prevent secondary pathogenesis, or damage that occurs after the initial insult; support regeneration and repair; and refine and optimize rehabilitation techniques.

### Traumatic Brain Injury

Greater access to and use of CT and MRI offer physicians the opportunity to diagnose the extent of tissue damage and determine medical management. In general, patients who arrive in the emergency room and are diagnosed with a severe head injury are monitored for pressure on the brain from bleeding or swelling. Treatments for increased intracranial pressure include the removal of *cerebrospinal fluid*, moderate

hyperventilation to temporarily decrease blood volume, and the administration of drugs to reduce cellular metabolism or to remove water from the injured tissue.

In addition to helping the physician avoid cerebral edema, or swelling as a result of excess accumulation of water in the brain, and reductions in cerebral blood flow following traumatic brain injury, imaging can reveal lesions produced by the initial injury. These lesions can consist of bleeding on the surface or within the brain as well as the formation of contusions, or bruises. Once blood leaks from vessels and comes into direct contact with brain tissue, it causes localized pressure, reducing cerebral blood flow. The blood itself also can be toxic to brain cells. Contusions can be troubling because they can increase pressure as well as contribute to the development of post-traumatic epilepsy. As a last resort to reduce increased intracranial pressure, part of the skull may be removed to allow the brain to swell, a procedure known as a decompressive craniectomy.

No drug for improving outcomes of traumatic brain injury has yet been approved. A recent pilot clinical trial for patients with moderate to severe closed-head injury found that the hormone progesterone cut the number of deaths in severely injured patients by 50 percent. Those in the moderately injured group had improved functional recovery 30 days after injury. Treatments for the injury-induced reduction of cerebral blood flow include the administration of drugs that increase mean arterial blood pressure. In combination with the reduction of intracranial pressure, this treatment results in an increase in blood flow, allowing more blood to reach vital areas.

### Spinal Cord Injury

Methylprednisolone is the only FDA-approved treatment for spinal cord injury. While there is increasing controversy about the use of this steroid, earlier studies showed efficacy when people with spinal cord injuries received high intravenous doses within eight hours of the injury. Building on these clues and insights into precisely how and why spinal cord cells die after injury, researchers hope to develop new therapies to reduce the extent of spinal cord damage after trauma. In that context, there is a growing interest in early intervention of the inflammatory response to prevent secondary damage by this response and support neurologic recovery.

Scientists have known that, after a spinal cord injury, animals can regain the ability to bear their weight and walk at various speeds on a treadmill belt. More recently, scientists have recognized that the level of this recovery depends to a large degree on whether these tasks are practiced — that is, trained for — after injury. People with spinal cord injury also respond to training interventions.

Scientists have also discovered that new nerve cells can be born in the adult brain, but these new cells do not seem sufficient to help the injured brain regenerate. Studies are underway to determine how to jump-start the pathway that stimulates neurogenesis, the birth of new nerve cells. Researchers are trying to decipher how certain environmental cues can be used or overcome to attract these new cells — or transplanted stem or progenitor cells — to areas of brain injury to facilitate regeneration and repair.

These and other recent discoveries are pointing the way toward new therapies to prevent secondary damage and promote nerve regeneration after brain and spinal cord injury. Although these new therapies have not yet reached the clinic, several of them are on the path to clinical trials.

## Pain

If there is a universal experience, it is pain. Each year, more than 76.2 million Americans suffer chronic, debilitating headaches or a bout with a bad back or the pain of arthritis — all at a total cost of some $100 billion. But it need not be that way. New discoveries about how chemicals in the body transmit and regulate pain messages have paved the way for new treatments for both chronic and acute pain.

### Treating Pain

Local anesthesia, or loss of sensation in a limited area of a person's body, is used to prevent pain during diagnostic procedures, labor, and surgical operations. Local anesthetics temporarily interrupt the action of all nerve fibers, including pain-carrying ones, by interfering with the actions of sodium channels. Historically, the most familiar of these agents was Novocain, which has been used by dentists for years. Lidocaine is more popular today.

Analgesia refers to the loss of pain sensation. The four main types of analgesics, or painkillers, are nonopioids, which refer to aspirin and related nonsteroidal anti-inflammatory drugs, or NSAIDs. Common NSAIDs include ibuprofen and naproxen. Opioids (morphine, codeine), antiepileptic agents (gabapentin, topiramate), and antidepressants (amitriptyline, duloxetine) are the other three types of analgesics. Acetaminophen, the active ingredient in Tylenol, has analgesic properties but does not reduce inflammation.

NSAIDs are useful for treating mild or moderate pain, such as headache, sprains, or toothache. Because NSAIDs

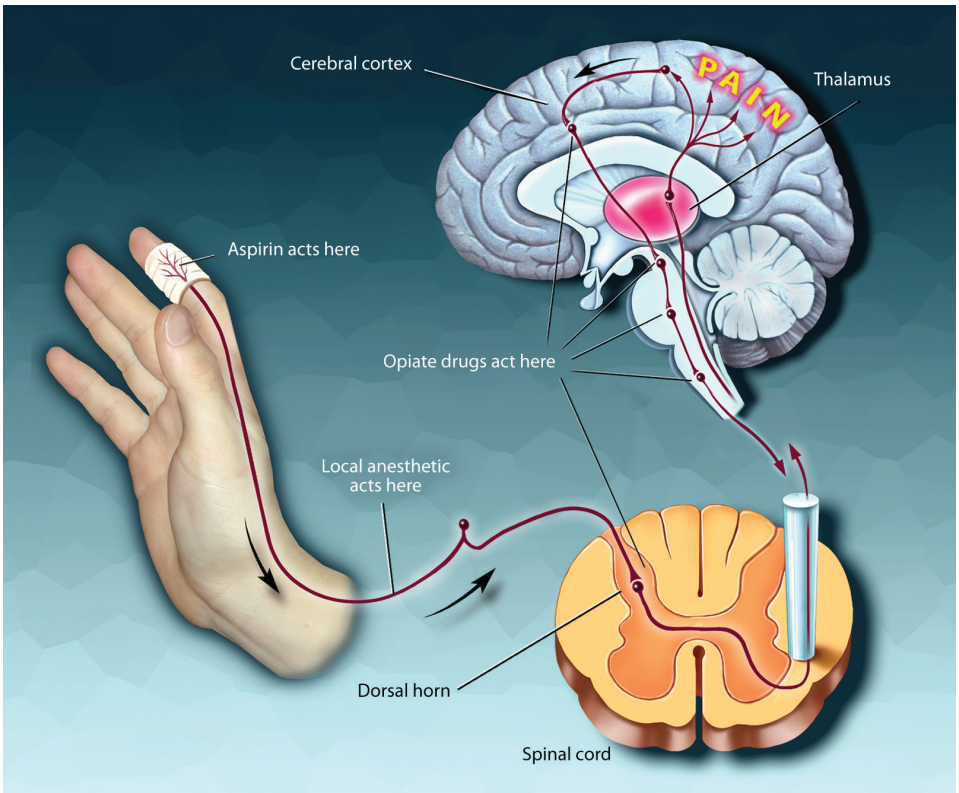
are anti-inflammatory, they also are effective for treating injuries or conditions such as arthritis and postoperative pain. NSAIDs work by inhibiting the cyclo-oxygenase (COX) enzymes that make the inflammatory and pain-producing chemical prostaglandin. Often moderate pain is treated by combining a mild opioid, such as codeine, with aspirin or an NSAID. Opioids are the most potent painkillers and are used for severe pain. Opioids, however, have many adverse side effects, such as respiratory depression and constipation, and in some individuals they have a high potential for abuse.

Antiepileptic and antidepressant drugs are useful primarily for neuropathic pain, which comes from injury to the nervous system. Such pain includes the pain from diabetic neuropathy, or damage to nerves in the body resulting from high blood sugar levels; neuralgia, or nerve pain or numbness, from viruses such as shingles; phantom limb pain; and post-stroke pain. The best results have been reported with antidepressants that regulate both serotonin and norepinephrine. Interestingly, SSRIs, which selectively affect serotonin, do not help relieve neuropathic pain. For some neuropathic pain conditions in which a light touch to the skin can produce severe pain, topical lidocaine may be effective.

### The Body's Pain-Control System

Studies of the body's own pain-control system not only demonstrated the existence of naturally occurring opioids — the endorphins — but also identified the receptors through which opioids exert their effects. The finding that opioid receptors are concentrated in the spinal cord led to the use of injections of morphine and other opioids into the cerebrospinal fluid in which the spinal cord is bathed, without causing paralysis, numbness, or other severe side effects. This technique came about through experiments with animals that first showed that injecting morphine into the spinal fluid could produce profound pain control. It is now commonly used in humans to treat pain after surgery, and to treat chronic pain in some patients by having them use an implanted pump.

New targets are on the horizon. Molecular biology and genetic approaches have identified many molecules, such as ion channels and receptors, which are predominantly, if not exclusively, expressed by the nociceptor, the peripheral nerve fiber that initially responds to the injury stimulus. Because adverse side effects of drugs arise from the widespread location of the molecules targeted by analgesics — for example, constipation results from morphine's action on opioid receptors in the gut — new analgesics that target only the nociceptor may have fewer side effects. Among the many nociceptor targets are specialized receptor channels — one of which is activated by capsaicin, the pungent ingredient in hot peppers, and another by mustard oil — as well as a variety of acid-sensing sodium and calcium ion channels. Blocking the activity of many of these molecules has proven effective in animal studies, suggesting that the development




At the site of an injury, the body produces prostaglandins, which increase pain sensitivity. Aspirin prevents the production of prostaglandins. Acetaminophen is believed to block pain impulses in the brain itself. Local anesthetics intercept pain signals traveling up the nerve. Opiate drugs, which act primarily in the central nervous system, block the transfer of pain signals from the spinal cord to the brain.

of drugs that target these molecules in humans may have great value for the treatment of acute and persistent pain. Following from these findings, topical (skin) application of high doses of capsaicin has recently been approved for some neuropathic pain conditions. This treatment likely kills the sensing portion of pain fibers, but because these nerve fibers will regenerate, treatment needs to be repeated.

Pain is a complex experience that is largely a product of brain function. The pain is in the brain, not in the nociceptors that respond to the injury. Pain also involves emotional factors, so previous experiences with pain can have an impact on a more recent experience. All of these variables must be addressed concurrently in order to treat pain. The fact that placebos and hypnosis can significantly reduce pain clearly illustrates the importance of these psychological factors.

## Seizures and Epilepsy

Seizures occur because of sudden, disorderly discharges of interconnected neurons in the brain that temporarily alter one or more brain functions. They are associated with epilepsy, a chronic neurological disorder characterized by the occurrence of unprovoked seizures. More than 50 million people have epilepsy worldwide, and 85 percent of those cases occur in developing countries. It is estimated that, globally, there are 2.4 million new cases each year.

Epilepsy can start at any age and be idiopathic — arising from an uncertain cause — or symptomatic — having a known or presumed cause. Most idiopathic epilepsies probably are due to the inheritance of one or more mutant genes, often a mutant ion channel gene. Symptomatic epilepsies result from a wide variety of brain diseases or injuries, including birth trauma, head injury, neurodegenerative disease, brain infection, brain tumor, or stroke.

Epilepsies can be either generalized or partial. Generalized seizures typically result in loss of consciousness and can cause a range of behavioral changes, including convulsions or sudden changes in muscle tone. They occur when there is simultaneous excessive electrical activity over a wide area of the brain, often involving the thalamus and cerebral cortex. Partial epilepsies, however, are characterized by seizures in which the individual maintains consciousness or has altered awareness and behavioral changes. Partial seizures can produce localized visual, auditory, and skin sensory disturbances; repetitive uncontrolled movements; or confused, automatic behaviors. Such seizures arise from excessive electrical activity in one area of the brain, such as a restricted cortical or hippocampal area.

Many antiepileptic drugs are available. Their principal targets are either ion channels or neurotransmitter receptors. Generalized epilepsies often are readily controlled by antiepileptic drugs, with up to 80 percent of patients seizure-free with treatment. Unfortunately, partial epilepsies are generally more difficult to treat. Often, they can be controlled with a single antiepileptic that prevents seizures or lessens their frequency, but sometimes a combination of these drugs is necessary. Identification of the mutated genes underlying epilepsy may provide new targets for the next generation of antiseizure drugs.

Surgery is an excellent option for patients with specific types of partial seizures who do not respond to antiepileptic drugs. Electrical recordings of brain activity from patients allow for precise localization of the brain area from which the partial seizures originate. Once this area has been found, neurosurgeons can then remove it. After surgery, most properly selected patients experience improvement or complete remission of seizures for at least several years.

A new form of epilepsy treatment, electrical stimulation therapy, was introduced as another option for hard-to-control partial seizures. An implanted device delivers small bursts of electrical energy to the brain via the vagus nerve on the side of the neck. While not curative, vagal nerve stimulation has been shown to reduce the frequency of partial seizures in many patients.

## Stroke

A stroke occurs when a blood vessel bringing oxygen and nutrients to the brain bursts or is clogged by a blood clot or some other particle. As a result, the brain is deprived of blood, causing the death of neurons within minutes. Depending on its location, a stroke can cause many permanent disorders, such as paralysis on one side of the body and loss of speech.

Until recently, if you or a loved one had a stroke, your doctor would tell your family there were few treatment options outside of physical or speech therapy. In all likelihood, the patient would live out the remaining months or years with severe neurological impairment.

This dismal scenario is now brightening. For one, use of the clot-dissolving bioengineered drug, tissue plasminogen activator (tPA), is now a standard treatment in many hospitals. This medication opens blocked vessels rapidly to restore circulation

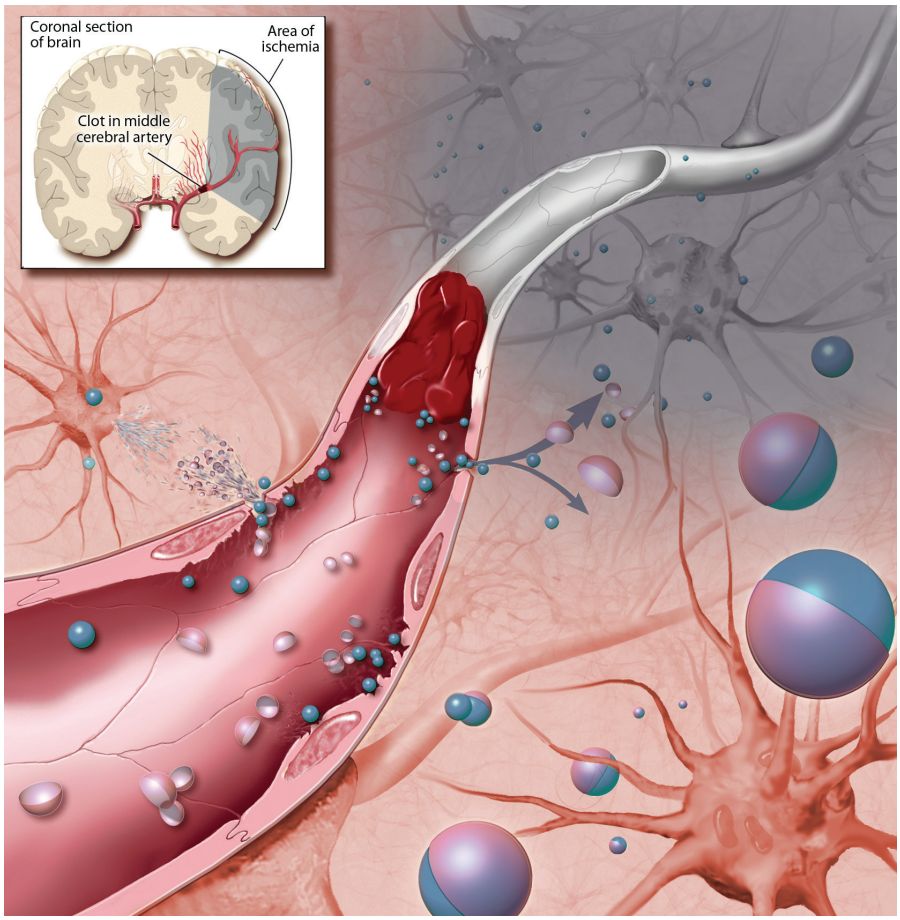
before oxygen loss causes permanent damage. Given within three hours of a stroke, it often can help in limiting the ensuing brain damage. Also, attitudes about the nation's third leading cause of death are changing rapidly. Much of this has come from new and better understanding of the mechanisms that lead to the death of neurons following stroke and the growing ability to devise ways to protect these neurons.

Stroke affects roughly 795,000 Americans a year — 137,000 of whom die as a result. The total annual costs are estimated at $73.7 billion. Stroke often occurs in individuals over 65 years of age, but a third of people who have strokes are younger. Stroke tends to occur more in males and African Americans as well as in those with risk factors such as diabetes, high blood pressure, heart disease, obesity, high cholesterol, and a family history of stroke.

Controlling risk factors with diet, exercise, and certain drugs may help prevent stroke. Other specific treatments involving surgery or arterial stents can clear clogs in the arteries of the neck region; these and other treatments targeting heart disease can help prevent a cutoff of blood supply. Anticoagulant drugs can reduce the likelihood of clots forming, traveling to the brain, and causing a stroke.

Other experimental therapies under investigation may lead to even bigger payoffs for patients in the future. Some strategies target mechanisms inside the neuron. In this way, the vicious cycle of local damage followed by a widening fringe of biochemical-induced neuronal death can be slowed. A number of classes of drugs have been shown to be effective in animal studies.

Emerging clinical evidence suggests that, following a stroke affecting movement in one arm, encouraging use of the weakened arm by temporarily restricting use of the unaffected arm may help functional recovery. Another promising possibility for improving recovery after stroke is through the use of neural stem cells. Some animal studies have shown that an injection of stem cells helps recovery even if administered several days after the injury. Administration of growth factors might further enhance the benefits of stem cell transplantation. Further research will indicate whether these therapies will translate from animals to humans.




A stroke occurs when a blood vessel bringing oxygen and nutrients to the brain bursts or is clogged by a blood clot, as shown in the image on the upper left. This lack of blood leads to a cascade of neurochemical abnormalities that can cause cell death within minutes. Free radicals are released, causing damage to endothelial cells and the mitochondria of neurons. Normally the body readily disarms free radicals, but in stroke, endothelial cell damage allows many more than can be controlled to move into brain tissue. Depending on its location, a stroke can result in different problems, such as paralysis on one side of the body or loss of speech.

# Chapter 15: Potential Therapies

## In this Chapter



## New Drugs

Most medicines used today were developed using trial-and-error techniques, which often do not reveal why a drug produces a particular effect. But the expanding knowledge gained from the methods of molecular biology — the ability to determine the structure of receptors or other proteins — makes it possible to design safer and more effective drugs.

In a test tube, the potency of an agent can be determined by how well it attaches to a receptor or other protein target. With this knowledge, scientists can vary the drug's structure to enhance its action on the desired target. Thus, subsequent generations of drugs can be designed to interact more selectively with the target or, in many cases, with specific subtypes of the target, producing better therapeutic effects and fewer side effects. While this rational drug design holds promise for developing drugs for conditions ranging from stroke and migraine headaches to depression and anxiety, it will take considerable effort to clarify the role of the different potential drug targets in these disorders.

Other promising candidates for drug therapies include growth, or trophic, factors; antibodies engineered to modify the interactions and toxicity of misfolded proteins, which are the cause of many neurodegenerative diseases; small molecules that take advantage of specific biochemical pathways; interfering RNAs (RNAi) that reduce toxic levels of individual proteins; and stem cells that could replace dead or dying neurons.

## Trophic Factors

One result of basic neuroscience research is the discovery of numerous trophic factors, which control the development and survival of specific groups of neurons. Once the specific actions of these molecules and their receptors are identified and their genes cloned, procedures can be developed to modify trophic factor-regulated functions in ways that might be useful in the treatment of neurological disorders. For example, copies of the factor might be genetically targeted to the area of the brain where this type of cell has died. The treatment may not cure a disease but could improve symptoms or delay the disease's progression.

Already, researchers have demonstrated the possible value of at least one of these factors, nerve growth factor (NGF). NGF slows the destruction of neurons that use acetylcholine. When infused into the brains of rats, NGF prevented cell death and stimulated the regeneration and sprouting of damaged neurons that are known to die in Alzheimer's disease. When aged animals with learning and memory impairments were treated with NGF, scientists found that these animals were able to remember a maze task as well as healthy aged rats. NGF also holds promise for slowing the memory deficits associated with normal aging.

Recently, several new factors have been identified. They are potentially useful for therapy, but scientists must first understand how they may influence neurons. In the future, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS) may be treated with trophic factors or their genes.

In an interesting twist on growth factor therapy, researchers have demonstrated that neutralizing molecules that stop or inhibit growth can help repair damaged nerve fiber tracts in the spinal cord. Using antibodies that override the effect of Nogo-A, a protein that inhibits

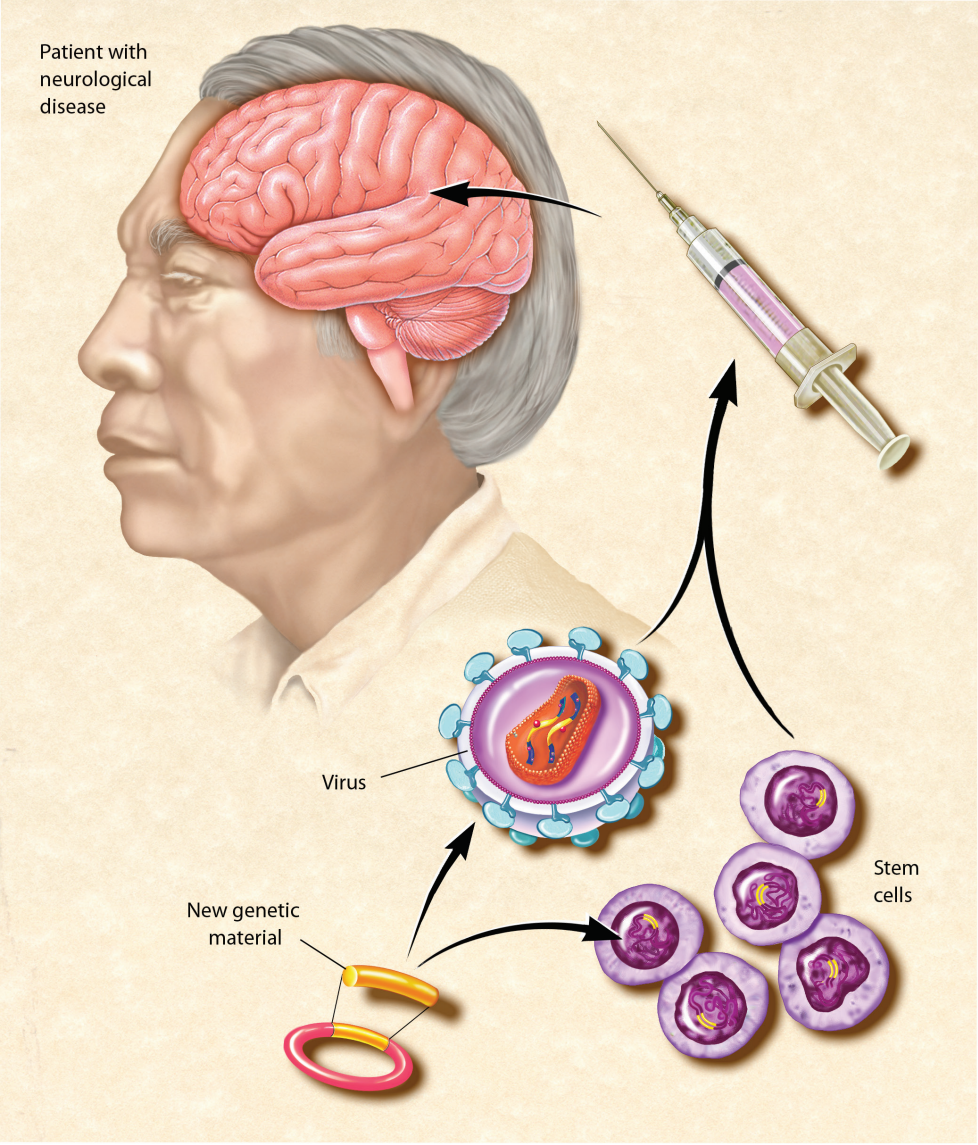
nerve regeneration, Swiss researchers succeeded in getting some nerves of damaged spinal cords to regrow in rats and monkeys. Treated animals of both species showed large improvements in their ability to walk and use their forepaw digits after spinal cord damage.

This research has been translated to a clinical setting, where recently injured spinal cord injury patients are being treated with anti-Nogo-A antibodies in a clinical trial.

## Engineered Antibodies

The immune system has evolved to target and modify factors both inside and outside of cells. It is sometimes possible to trick the immune system into attacking those proteins that cause neurological diseases by "vaccinating" patients against them. This approach has shown some promise in treating Alzheimer's disease, although it also carries risks, such as increased inflammation when the brain reacts to the antibodies against its proteins. Another new approach combines genetic engineering with immunology to engineer antibodies or fragments of antibodies that can bind to and alter the disease characteristics of specific proteins. These therapies could be delivered either as proteins or as genes.

Therapies such as these have produced promising preliminary results for Huntington's, Parkinson's, and Alzheimer's diseases, as well as neurodegenerative disorders such as variant Creutzfeldt-Jakob disease (vCJD), known as prion diseases. vCJD has been linked to bovine spongiform encephalitis, or mad cow disease. In experiments with fruit




Therapies like stem cells and gene therapy may one day help combat disease. Researchers hope stem cells will incorporate into the brain to replace diseased or injured cells. Similarly, they are studying a variety of viruses that could carry therapeutic genes into the brain to correct nervous system diseases and disorders.

*Researchers are pursuing a variety of new ways to repair or replace neurons and other cells in the brain.*

flies (*Drosophila*), those modified to carry the mutant human gene for Huntington's disease are generally too weak and uncoordinated to break out of their pupal case, the way normal insects do. However, when they are treated so that they also express the gene for an anti-HD antibody, all of them emerge as young adults. Furthermore, these treated flies live longer than the untreated ones that do manage to emerge, and the treated ones show less pathology in their brains.

## Small Molecules and RNAs

As our understanding of the processes that underlie brain damage progresses, it is becoming possible to use small-molecule drugs, such as antibiotics and anti-tumor drugs, to alter these processes. Scientists have had some success developing animal models that are treated with these drugs, which appear to reduce the neuronal damage in ALS, Huntington's disease, and Parkinson's disease.

Thousands of small-molecule drug candidates can be tested using high-throughput screening, during which hundreds or thousands of compounds are tested to find those with the desired cellular effect. This process has been used to find therapies for neurodegenerative diseases. Because many of these diseases involve proteins that misfold and clump abnormally, lasers are used to measure whether proteins are clumped inside cells that have been robotically distributed into tiny containers, along with the small molecules to be tested. A machine then scans the containers and reports whether particular drugs have changed the protein clumping. Those drugs that are identified can then be tested further. New leads for drugs to treat Alzheimer's and prion diseases have recently been described using these methods.

Several neurodegenerative diseases are caused by the accumulation of abnormal proteins. If the cells made many fewer such proteins, then the disease presumably would progress much more slowly. A new class of potential drugs is based on removing the RNAs that code for the proteins that are causing damage. Mouse models of Huntington's disease and ALS appear to have responded positively to such treatments, which are delivered via gene therapies.

## Cell and Gene Therapy

Researchers throughout the world are pursuing a variety of new ways to repair or replace neurons and other cells in the brain. For the most part, these experimental approaches are still being worked out in animals and cannot be considered therapies for humans at this time.

Scientists have identified neuronal stem cells — unspecialized cells that give rise to cells with specific functions — in the brain and spinal cord of embryonic and adult mice. Stem cells can continuously produce all three major cell types of the brain: neurons; astrocytes, the cells that nourish and protect neurons; and oligodendrocytes, the cells that surround axons and allow them to conduct their signals efficiently. The production abilities of stem cells may someday be useful for replacing brain cells lost to disease. Recently, scientists have discovered how to convert cells from adult tissue into stem cells, raising the possibility that they might be pharmacologically directed to replace damaged neurons tailored to a specific patient and disease.

In other work, researchers are studying a variety of viruses that can carry therapeutic genes into the brain to correct nervous system diseases. Studies in animal models of human diseases have shown that gene transfer vectors can be effective in correcting at least some aspects of neurological disease. At this time, adeno-associated virus (AAV) and lentivirus seem to be the safest and most efficient vectors. These vectors are being used in clinical trials in patients with Parkinson's and in some rare genetic diseases. Herpes simplex virus and adenovirus vectors have been evaluated in early-stage human trials for treating brain tumors.

# Chapter 16: Neuroethics

## In this Chapter



Breaking a confidence. Going along to get along. Telling a white lie to protect a friend. Everyone faces ethical dilemmas — in school, at home, and nearly everywhere in everyday life.

Neuroscientists are no different. With tremendous advances in the field, scientists and nonscientists alike have sensed a critical turning point. Advancing knowledge about how the brain controls normal behavior; how injury, drugs, or disease affect it; and how diagnoses and treatments could change brain function raises serious and novel ethical questions.

For example, some recent brain imaging studies have sought to define the processes responsible for phenomena such as deception. The post-9/11 era has created much interest in lie detection equipment that could be used to screen airline passengers for security purposes. Is the technology accurate enough to provide useful data upon which to base decisions? How should privacy be balanced with security? Pursuing these lines of scientific inquiry in a responsible way requires neuroscientists to examine how what they do affects the world beyond the laboratory or clinic.

This kind of questioning makes up a field known as neuroethics. Scientists and ethicists are beginning to reflect on the implications of neuroscience in areas of behavioral research, such as moral reasoning and decision-making, as well as the implications of new neuroscience technologies, including brain scanning, brain stimulation, and pharmaceuticals, which can manipulate cognition. While many questions and methods within neuroethics are similar to those in biomedical ethics, neuroethics deals with brain-specific issues that touch no other area of science — our sense of self, our personalities, and our behavior. Furthermore, brain science is developing interventions that can change the way our brains function. Neuroethics links the science — what we can do — with the question of what we should do, which is guided by individual and shared value systems.

Neuroethics is the subject of a growing body of literature and an increasing number of meetings and conferences that have attracted a wide range of thinkers, students, basic and clinical neuroscientists, economists, philosophers, journalists, sociologists, lawyers, judges, and others. Included among the major topics under discussion are those listed below.

## Personal Responsibility and Punishment

Neuroscience is teaching us about the neural substrates of human characteristics, such as anger, impulse control, and conscience. It is also giving us insight into the brain mechanisms of conditions such as addiction and other disorders that impair behavioral control. These discoveries will shed new light on traditional questions of personal responsibility. Our understanding of the brain as the control center for all decisions and actions challenges the concept of free will as the basis for personal responsibility. As a result, questions emerge such as the following: If the brain is the source of all action, do we hold the person less responsible for his actions when the brain is damaged? Does antisocial behavior itself provide evidence of a maladapted or miswired brain, or do we need physical evidence of trauma or disease?

Neuroscience is not only interested in questions about criminal behavior, but also in questions about how more normal members of society create and enforce the laws

that criminals violate. Some commentators think that increasing neuroscience knowledge may seriously challenge fundamental tenets of criminal law, while others foresee incremental changes that may lead to more just, accurate, and fair judgments. Neuroethics can help society think about how newfound knowledge of the brain as the basis of behavior may affect our ideas of the way society should function.

## Diagnosis, Treatment, and Enhancement

Neuroscience already has given rise to drugs and devices, developed for the treatment of illness, that permit healthy people to improve their cognitive performance or alter their emotional states. In the future, drugs may be developed that enhance memory or alter social behaviors. It is critical that scientists engage policymakers and society at large in discussions about the extension of treatments from the realm of illness to the realm of enhancement. Neuroethical issues in medicine arise when gaps exist between diagnosis and treatment, treatments may offer tradeoffs in personality or cognitive changes, and drugs or devices that can help unwell patients also can boost performance of normal people.

For example, when diagnostic tests exist for brain-based diseases that have no cure, such as Alzheimer's, how should the tests be used? Should emergency rooms administer memory-altering drugs to patients who have suffered a trauma and may be at risk for post-traumatic stress disorder? If drugs that are effective for treating attention deficit hyperactivity disorder also improve work or classroom performance of normal people, do we need to regulate access, and do we consider such use to be cheating? More questions of this type will emerge as our knowledge increases.

## Social Behavior

The neurobiological basis of social interaction is now an exciting topic of research. While a major goal of such research is the treatment of disabling conditions such as autism spectrum disorders, the knowledge gleaned may also permit us to delve into other kinds of social behavior. Already, it is possible to use brain imaging to observe emotional responses, including such morally freighted responses as negative reactions to members of minority groups within a society. How should we use such information? Will it help us understand prejudice, or could it be used to influence decisions about individuals? It is critical that scientists explain the limitations of current technologies and help formulate policies to minimize the chances of misuse.

## Predicting Behavior

Neuroimaging and genetic screening may enable us to predict behavior, personality, and disease with greater accuracy than ever before. Neuroimaging technology is also being researched and marketed for lie detection for consumer targets, including national security, employment screening, the legal system, and personal relationships. As individuals and members of groups, people have long been interested in predicting someone else's behavior or detecting whether or not they are truthful.

*Neuroethics links the science — what we can do — with the question of what we should do.*

Neuroscience technologies that enable more accurate assessment of behavior also raise important concerns about privacy and fairness that go beyond those in bioethics. For example: Will we be able to use imaging to measure intelligence? Empathy? Risk for violence? What degree of privacy do we expect to have over our thoughts? If someone has not yet committed a crime but shows inappropriate brain-based reactions, such as sexual responses to pictures of children, would we require further monitoring or even preventive detention? The neuroimaging detection of lying has the potential to have a major impact on society but will require careful controls and years of further research before its validity can be established. People lie for different reasons under different circumstances, not all lies cause harm, and even brain correlates of deception will never give us an objective determination of truth. Predicting individual behavior and determining truthfulness will be major areas of research in neuroimaging and behavioral neuroscience in the coming years, and neuroethics will face many challenges as technologies evolve.

## Informed Consent in Research

Special care must be taken when scientists seek consent to conduct human research and throughout experiments, especially when potential research subjects have thinking or emotional impairments that might affect their decision-making capacity. Consent is an ongoing process that should involve education of the potential research participant and, when appropriate, family members. Researchers are discussing potential needs to exercise greater scrutiny, ensure safeguards, and enhance participants' grasp of a study, including risks and benefits.

## Effective and Ethical Science: Communication and Commercial Enterprise

Neuroethics will draw from the experience of bioethics in handling scientific communication with the media and responsible transfer of knowledge from basic science to profit-driven venture. A major concern for neuroethicists is the degree to which the media and the public's fascination with neuroscience can lead to overstatements and inaccuracies in media communication. Early studies have shown that neuroscience information and pictures of brain images lend excessive credibility to scientific statements in the media, which may underscore "neurorealism" — the idea that anything neuroscientific must be definitive and true. The powerful allure of neuroscience may also entice commercialization of neurotechnologies before the risks, benefits, and limitations of the science are fully understood. Neuroethics has a critical role in protecting the integrity of neuroscience by promoting responsible and accurate scientific communication in the media; supporting appropriate oversight of commercialized neurotechnologies, including accurate advertising; and urging proactive communication in the popular media to promote public discussion of ethical, social, and legal issues arising from neuroscience knowledge and technology.

At this stage, the field of neuroethics raises more questions than it answers. It poses challenges to scientists, ethicists, lawyers, policy-makers, and the public as they strive to work through the social implications of new discoveries. The issues are too broad-based to expect that scientists alone will supply the answers. But neuroscientists are well positioned to help shape and contribute to the debate and discussion.

One of the hallmarks of neuroscience has been the drive toward integrating information from disparate fields and specializations to increase knowledge. Sorting through the complex issues captured under the umbrella of neuroethics provides an important opportunity for informed and rich discussions among scientists and with the public. Continuing study of neuroethics will help all segments of society deal with the challenges posed by emerging technologies that investigate the brain and how it works.

# Brain Facts Glossary

Acetylcholine A critical neurotransmitter that controls functions such as memory, attention, sleep, heart rate, and muscular activity.

Action Potential An electrical charge that travels along the axon to the neuron's terminal, where it triggers the release of a neurotransmitter. This occurs when a neuron is activated and temporarily reverses the electrical state of its interior membrane from negative to positive.

Adenosine A neurochemical that inhibits wakefulness, serving the purpose of slowing down cellular activity and diminishing arousal. Adenosine levels decrease during sleep.

Adrenal Cortex An endocrine organ that secretes steroid hormones for metabolic functions; for example, in response to stress.

Adrenal Medulla An endocrine organ that secretes epinephrine and norepinephrine in concert with the activation of the sympathetic nervous system; for example, in response to stress.

Agonist 1.) A neurotransmitter, drug, or other molecule that stimulates receptors to produce a desired reaction. 2.) A muscle that moves a joint in an intended direction.

Alzheimer's Disease A major cause of dementia in the elderly, this neurodegenerative disorder is characterized by the death of neurons in the hippocampus, cerebral cortex, and other brain regions. The earliest symptoms of the disease include forgetfulness; disorientation as to time or place; and difficulty with concentration, calculation, language, and judgment. In the final stages, individuals are incapable of self-care and may be bedridden.

Amino Acid Transmitters The most prevalent neurotransmitters in the brain, these include glutamate and aspartate, which have excitatory actions on nerve cells, and glycine and gamma-aminobutyric acid (GABA), which have inhibitory actions on nerve cells.

Amygdala A structure in the forebrain that is an important component of the limbic system and plays a central role in emotional learning, particularly within the context of fear.

Amyotrophic Lateral Sclerosis (ALS) Commonly known as Lou Gehrig's disease, ALS causes motor neurons in the brain and spinal cord to disintegrate, resulting in loss of control of voluntary muscle movements such as walking.

Androgens Sex steroid hormones, including testosterone, found in higher levels in males than females. They are responsible for male sexual maturation.

Antagonist 1.) A drug or other molecule that blocks receptors. Antagonists inhibit the effects of agonists. 2.) A muscle that moves a joint in opposition to an intended direction.

Aphasia Disturbance in language comprehension or production, often as a result of a stroke.

Apoptosis Programmed cell death induced by specialized biochemical pathways, often serving a specific purpose in the development of an animal.

Auditory Nerve A bundle of nerve fibers extending from the cochlea of the ear to the brain that contains two branches: the cochlear nerve, which transmits sound information, and the vestibular nerve, which relays information related to balance.

Attention Deficit Hyperactivity Disorder (ADHD) A condition characterized by excessively inattentive, hyperactive, or impulsive behaviors.

Autism Spectrum Disorders (ASD) A condition characterized by impaired social skills; verbal and nonverbal communication difficulties; and narrow, obsessive interests or repetitive behaviors.

Autonomic Nervous System A part of the peripheral nervous system responsible for regulating the activity of internal organs. It includes the sympathetic and parasympathetic nervous systems.

Axon The fiberlike extension of a neuron by which it sends information to target cells.

Basal Ganglia Structures located deep in the brain that play an important role in the initiation of movements. These clusters of neurons include the caudate nucleus, putamen, globus pallidus, and substantia nigra. Cell death in the substantia nigra contributes to Parkinson's disease.

Bipolar Disorder Previously known as manic-depressive illness, this disorder is characterized by episodes of deep depression and manic highs. The depressive episodes are similar to those experienced by people with depression. Symptoms of mania include increased energy, decreased need for sleep, a marked interest in goal-directed activities, and poor judgment.

**Brainstem** The major route by which the forebrain sends information to and receives information from the spinal cord and peripheral nerves. The brainstem controls, among other things, respiration and the regulation of heart rhythms.

**Broca's Area** The brain region located in the frontal lobe of the left hemisphere that is important for the production of speech.

**Catecholamines** The neurotransmitters dopamine, epinephrine, and norepinephrine, which are active in both the brain and the peripheral sympathetic nervous system. These three molecules have certain structural similarities and are part of a larger class of neurotransmitters known as monoamines.

**Cell Body** The part of a neuron that contains the nucleus (with DNA) and the organelles, but not the projections such as the axon or dendrites.

**Cerebrum** The largest part of the human brain associated with higher order functioning, such as thinking, perceiving, planning, and understanding language, as well as the control of voluntary behavior.

**Cerebellum** A large structure located at the roof of in the hindbrain that helps control the coordination of movement by making connections to the pons, medulla, spinal cord, and thalamus. It also may be involved in aspects of motor learning.

**Cerebral Cortex** A sheet of tissue covering the outermost layer of the cerebrum.

**Cerebrospinal Fluid** A liquid found within the ventricles of the brain and the central canal of the spinal cord.

**Circadian Rhythm** A cycle of behavior or physiological change lasting approximately 24 hours.

**Cochlea** A snail-shaped, fluid-filled organ of the inner ear responsible for converting sound into electrical potentials to produce an auditory sensation.

**Cognition** The process or processes by which an organism gains knowledge or becomes aware of events or objects in its environment and uses that knowledge for comprehension and problem-solving.

**Cone** A primary receptor cell for vision located in the retina. It is sensitive to color and is used primarily for daytime vision.

**Corpus Callosum** The large bundle of nerve fibers linking the left and right cerebral hemispheres.

**Cortisol** A hormone manufactured by the adrenal cortex. In humans, cortisol is secreted in the greatest quantities before dawn, readying the body for the activities of the coming day.

**Cranial Nerve** A nerve that carries sensory and motor output for the head and neck region. There are 12 cranial nerves.

**Declarative Memory** The ability to learn and consciously remember everyday facts and events.

**Depression** A psychiatric disorder characterized by sadness, hopelessness, pessimism, loss of interest in life, reduced emotional wellbeing, and abnormalities in sleep, appetite, and energy level.

**Dendrite** A treelike extension of the neuron cell body. The dendrite is the primary site for receiving and integrating information from other neurons.

**Dopamine** A catecholamine neurotransmitter present in three circuits of the brain: one that regulates movement; a second thought to be important for cognition and emotion; and a third that regulates the endocrine system. Deficits of dopamine in the motor circuit are associated with Parkinson's disease. Abnormalities in the second circuit have been implicated in schizophrenia.

**Down Syndrome** A condition that typically occurs when, at the time of conception, an extra copy of chromosome 21 is present in the egg. This genetic anomaly is associated with physical and developmental characteristics, including mild to moderate intellectual disabilities; low muscle tone; and an increased risk of congenital heart defects, respiratory problems, and digestive tract obstruction.

**Drug Addiction** Loss of control over drug intake or compulsive seeking and taking of drugs, despite adverse consequences.

**Endocannabinoids** Lipid-derived messengers sometimes referred to as the brain's marijuana. These messengers control the release of neurotransmitters, usually by inhibiting them, and can affect the immune system and other cellular parameters. Endocannabinoids also play an important role in the control of behaviors.

**Electroencephalography (EEG)** A technology used to record electrical activity of the human brain in response to a variety of stimuli and activities.

**Endocrine Gland** An organ that secretes a hormone directly into the bloodstream to regulate cellular activity of certain other organs.

**Endorphins** Neurotransmitters produced in the brain that generate cellular and behavioral effects like those of morphine.

**Epilepsy** A disorder characterized by repeated seizures, which are caused by abnormal excitation of large groups of neurons in various brain regions. Epilepsy can be treated with many types of anticonvulsant medications.

**Epinephrine** A hormone, released by the adrenal medulla and specialized sites in the brain. During times of stress, epinephrine, also known as adrenaline, is quickly released into the bloodstream. It then serves to put the body into a general state of arousal, which enables it to cope with the challenge.

**Estrogens** A group of sex hormones found more abundantly in females than males. They are responsible for female sexual maturation and other functions.

**Excitation** A change in the electrical state of a neuron that is associated with an enhanced probability of action potentials.

**Follicle-Stimulating Hormone** A hormone released by the pituitary gland that stimulates the production of sperm in the male and growth of the follicle (which produces the egg) in the female.

**Forebrain** The largest part of the brain, which includes the cerebral cortex and basal ganglia. The forebrain is credited with the highest intellectual functions.

**Fovea** The centermost part of the eye located in the center of the retina and contains only cone photoreceptors.

**Frontal Lobe** One of the four subdivisions of the cerebral cortex. The frontal lobe has a role in controlling movement and in the planning and coordinating of behavior.

**Functional Magnetic Resonance Imaging (fMRI)** A technology that uses magnetic fields to detect activity in the brain by monitoring blood flow.

**Gamma-aminobutyric Acid (GABA)** An amino acid transmitter in the brain whose primary function is to inhibit the firing of nerve cells.

**Glia** Specialized cells that nourish and support neurons.

**Glucocorticoids** Hormones that produce an array of effects in response to stress. Some of the actions of glucocorticoids help mediate the stress response, while other, slower actions counteract the primary response to stress and help re-establish homeostasis.

**Glutamate** An amino acid neurotransmitter that acts to excite neurons. Glutamate stimulates N-methyl-d-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA). AMPA receptors have been implicated in activities ranging from learning and memory to development and specification of nerve contacts in developing animals. Stimulation of NMDA receptors may promote beneficial changes, whereas overstimulation may be a cause of nerve cell damage or death in neurological trauma and stroke.

**Gonad** Primary sex gland: testis in the male and ovary in the female.

**Gray Matter** Portions of the brain that are gray in color because they are composed mainly of neural cell bodies, rather than myelinated nerve fibers, which are white.

**Growth Cone** A distinctive structure at the growing end of most axons. It is the site where new material is added to the axon.

**Hair Cells** Sensory receptors in the cochlea that convert mechanical vibrations to electrical signals; they in turn excite the 30,000 fibers of the auditory nerve that carry the signals to the brainstem.

**Hindbrain** The most posterior part of the brain comprises the pons, medulla oblongata, and cerebellum.

**Hippocampus** A seahorse-shaped structure located within the brain and considered an important part of the limbic system. One of the most studied areas of the brain, it is involved in learning, memory, and emotion.

**Homeostasis** The normal equilibrium of body function.

**Hormones** Chemical messengers secreted by endocrine glands to regulate the activity of target cells. They play a role in sexual development, calcium and bone metabolism, growth, and many other activities.

**Huntington's Disease** A genetic disorder characterized by involuntary jerking movements of the limbs, torso, and facial muscles, often accompanied by mood swings, depression, irritability, slurred speech, and clumsiness.

**Hypothalamus** A complex brain structure composed of many nuclei with various functions, including regulating the activities of internal organs, monitoring information from the autonomic nervous system, controlling the pituitary gland, and regulating sleep and appetite.

**Interneuron** A neuron that exclusively signals another neuron.

Inhibition A synaptic message that prevents a recipient neuron from firing.

Ions Electrically charged atoms or molecules.

Ion Channels Selectively permeable water-filled channels that pass through the cell membrane and allow ions or other small molecules to enter or leave the cell.

Long-Term Memory The final phase of memory, in which information storage may last from hours to a lifetime.

Magnetic Resonance Imaging (MRI) A technique that uses magnetic fields to create a high-quality, three-dimensional image of organs and structures inside the body. This technology is noninvasive and does not expose the body to X-rays or other radiation.

Magnetic Resonance Spectroscopy (MRS) Using the same machinery as MRI, MRS measures the concentration of certain chemicals, such as neurotransmitters, instead of blood flow.

Magnetoencephalography (MEG) A technique that can quantitatively measure the strength of activity in various regions of the brain at millisecond resolution.

Metabolism The sum of all physical and chemical changes that take place within an organism and all energy transformations that occur within living cells.

Midbrain The most anterior segment of the brainstem. With the pons and medulla, the midbrain is involved in many functions, including regulation of heart rate, respiration, pain perception, and movement.

Migration The process whereby new neurons find their proper position in the brain.

Mitochondria Small cylindrical organelles inside cells that provide energy for the cell by converting sugar and oxygen into special energy molecules, called adenosine triphosphate (ATP).

Motor Neuron A neuron that carries information from the central nervous system to muscle.

Motor Unit A functional unit made up of an alpha motor neuron and all the muscle fibers it contains and controls, ranging from a few to a hundred or more.

Mutations Changes in DNA, such as "misspellings" in the gene sequence or incorrect amounts of DNA, that can prevent a gene from functioning properly.

Multiple Sclerosis (MS) An autoimmune disease in which the body's natural defenses attack the myelin sheath covering the axons of neurons in the central nervous system. Symptoms include numbness, clumsiness, and blurred vision.

Myasthenia Gravis A disease in which acetylcholine receptors on muscle cells are destroyed so that muscles can no longer respond to the acetylcholine signal to contract. Symptoms include muscular weakness and progressively more common bouts of fatigue. The disease's cause is unknown but is more common in females than in males; it usually strikes between the ages of 20 and 50.

Myelin Sheath Compact fatty material that surrounds and insulates the axons of some neurons and accelerates the transmission of electrical signals.

NMDA Receptors N-methyl-d-aspartate (NMDA) receptors, one of three major classes of glutamate receptors, which have been implicated in activities ranging from learning and memory to development and specification of nerve contacts in a developing animal.

Nerve Growth Factor A substance whose role is to guide neuronal growth during embryonic development, especially in the peripheral nervous system. Nerve growth factor also probably helps sustain neurons in the adult.

Nerve Terminal The tip of the axon where neurotransmitters are released.

Neural Induction The process during embryonic development whereby molecules trigger ectoderm tissue to become nerve tissue.

Neurogenesis The production and growth of new nerve cells during development and, in select brain regions, throughout life.

Neuron A nerve cell specialized for the transmission of information and characterized by long, fibrous projections called axons and shorter, branchlike projections called dendrites.

Neuroscientist Scientists who specialize in the study of the brain and the nervous system.

Neurotransmitter A chemical released by neurons at a synapse for the purpose of relaying information to other neurons via receptors.

Nociceptors In animals, nerve endings that signal the sensation of pain. In humans, they are called pain receptors.

Norepinephrine A catecholamine neurotransmitter produced both in the brain and in the peripheral nervous system. Norepinephrine is involved in arousal and sleep regulation, mood, and blood pressure.

Occipital Lobe One of the four subdivisions of the cerebral cortex. The occipital lobe plays a role in processing visual information.

Olfactory Bulb A round, knoblike structure of the brain responsible for processing the sense of smell. Specialized olfactory receptor cells are located in a small patch of mucous 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 on top of the bone.

Orexin Neurons Specialized neurons that provide an excitatory signal to the arousal system, particularly to the norepinephrine neurons. Orexin activation plays a critical role in preventing abnormal transitions into REM sleep during the day, as occurs in narcolepsy.

Parasympathetic Nervous System A branch of the autonomic nervous system concerned with the conservation of the body's energy and resources during relaxed states.

Parietal Lobe One of the four subdivisions of the cerebral cortex. The parietal lobe plays a role in sensory processes, attention, and language.

Parkinson's Disease A movement disorder caused by death of dopamine neurons in the substantia nigra, located in the midbrain. Symptoms include slowness of movement, muscular rigidity, and walking and balance impairment.

Peptides Chains of amino acids that can function as neurotransmitters or hormones.

Peripheral Nervous System A division of the nervous system consisting of all nerves that are not part of the brain or spinal cord.

Photoreceptor A nerve ending, cell, or group of cells specialized to sense or receive light.

Pituitary Gland An endocrine organ closely linked with the hypothalamus. In humans, the pituitary gland is composed of two lobes and secretes several different hormones that regulate the activity of other endocrine organs throughout the body.

Plasticity The ability of the brain to modify its neural connections to adapt to challenges in the environment.

Pons A part of the hindbrain that, with other brain structures, controls respiration and regulates heart rhythms. The pons is a major route by which the forebrain sends information to and receives information from the spinal cord and peripheral nervous system.

Positron Emission Tomography (PET) A method of measuring brain function based on the detection of radioactivity emitted when positrons, positively charged particles, undergo radioactive decay in the brain. Computers then build three-dimensional images of changes in blood flow based on the amount of radiation emitted in different brain regions. The more brain activity, the more vivid the picture that is created.

Psychosis A severe symptom of psychiatric disorders characterized by an inability to perceive reality. Psychosis can occur in many conditions, including schizophrenia, bipolar disorder, depression, and drug-induced states.

Rapid Eye Movement (REM) Sleep Part of the sleep cycle when active dreaming takes place. It is characterized by neocortical EEG waves similar to those observed during waking. This state is accompanied by paralysis of the body's muscles; only the muscles that allow breathing and control eye movements remain active.

Reflexes Considered the simplest and most fundamental movements, they 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.

Retina A multilayered sensory tissue that lines the back of the eye and contains the receptor cells to detect light.

Reuptake A process by which released neurotransmitters are absorbed for later reuse.

Rod A sensory neuron located in the periphery of the retina. The rod is sensitive to light of low intensity and is specialized for nighttime vision.

Schizophrenia A chronic disorder characterized by psychosis (e.g., hallucinations and delusions), flattened emotions, and impaired cognitive function.

Second Messengers Substances that trigger communication after the actions of neurotransmitters at their receptors have been completed. 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.

Serotonin A monoamine neurotransmitter believed to play many roles, including but not limited to temperature regulation, sensory perception, and the onset of sleep. Neurons using serotonin as a transmitter are found in the brain and gut. Several antidepressant drugs are targeted to brain serotonin systems.

Short-Term Memory A phase of memory in which a limited amount of information may be held for several seconds or minutes.

Spinal Cord The extension of the brain through the vertebral column that primarily functions to facilitate communication between the brain and the rest of the body.

Stem Cell Unspecialized cells that renew themselves for long periods through cell division.

Stimulus An environmental event capable of being detected by sensory receptors.

Stress Any external stimulus that threatens homeostasis — the normal equilibrium of body function. Many kinds of stress have a negative effect on the body, but some kinds can be helpful.

Stroke A block in the brain's blood supply. A stroke can be caused by the rupture of a blood vessel, a clot, or pressure on a blood vessel (as by a tumor). Without oxygen, neurons in the affected area die, and the part of the body controlled by those cells cannot function. A stroke can result in loss of consciousness and death.

Suprachiasmatic Nucleus A small group of nerve cells in the hypothalamus that express clock proteins, which go through a biochemical cycle of about 24 hours. This sets the pace for daily cycles of activity, sleep, hormone release, and other bodily functions.

Sympathetic Nervous System A branch of the autonomic nervous system responsible for mobilizing the body's energy and resources during times of stress and arousal.

Synapse A physical gap between two neurons that functions as the site of information transfer from one neuron to another.

Taste Bud A sensory organ found on the tongue.

Temporal Lobe One of the four major subdivisions of each hemisphere of the cerebral cortex. The temporal lobe functions in auditory perception, speech, and complex visual perceptions.

Thalamus A structure consisting of two egg-shaped masses of nerve tissue, each about the size of a walnut, deep within the brain. The key relay station for sensory information flowing into the brain, the thalamus filters out information of particular importance from the mass of signals entering the brain.

Trophic Factors Small proteins in the brain that are necessary for the development, function, and survival of specific groups of neurons.

Ventricles Comparatively large spaces filled with cerebrospinal fluid. Of the four ventricles, three are located in the forebrain and one in the brainstem. The lateral ventricles, the two largest, are symmetrically placed above the brainstem, one in each hemisphere.

Vertebral Column The column of bones, or vertebrae, that extends down the back and functions as a structural element for the body while also surrounding and protecting the spinal cord.

Wernicke's Area A brain region responsible for comprehension of language and production of meaningful speech.

White Matter The part of the brain that contains myelinated nerve fibers. The white matter gets its color from myelin, the insulation covering nerve fibers.

# Neuroscience Resources

## The Society for Neuroscience
1121 14th Street, NW
Washington, DC 20005
(202) 962-4000
www.sfn.org

## Neuroscience Partner Organizations

### Canadian Association for Neuroscience
www.can-acn.org

### Canadian Institutes of Health Research
(613) 941-2672
www.cihr-irsc.gc.ca

### Dana Alliance for Brain Initiatives
(212) 223-4040
www.dana.org

### Faculty for Undergraduate Neuroscience
www.funfaculty.org

### Federation of European Neuroscience Societies
+49 (0) 30 9406 3133/3336
www.fens.org

### Foundation for Biomedical Research
(202) 457-0654
www.fbresearch.org

### International Brain Research Organization
www.ibro.org

### La Sociedad Mexicana de Ciencias Fisiológicas (Mexican Society of Physiological Sciences)
www.smcf.org.mx

### Wellcome Trust
+44 (0)20 7611 8888
www.wellcome.ac.uk

## U.S. National Institutes of Health (NIH)
(301) 496-4000
www.nih.gov

## NIH Institutes and Centers

### National Eye Institute
(301) 496–2234
www.nei.nih.gov

### National Heart, Lung and Blood Institute
(301) 592–8573
www.nhlbi.nih.gov

### National Institute on Aging
(301) 496–9265
www.nia.nih.gov

### National Institute on Alcohol Abuse and Alcoholism
(301) 443–3885
www.niaaa.nih.gov

### National Institute of Biomedical Imaging and Bioengineering
(301) 451–6768
www.nibib.nih.gov

### National Institute of Child Health and Human Development
(301) 496–3454
www.nichd.nih.gov

### National Institute on Deafness and Other Communication Disorders
(301) 402–0900
www.nidcd.nih.gov

### National Institute of Dental and Craniofacial Research
(301) 496–3571
www.nidcr.nih.gov

### National Institute on Drug Abuse
(301) 443–6480
www.nida.nih.gov

### National Institute of Environmental Health Sciences
(919) 541–3201
www.niehs.nih.gov

### National Institute of General Medical Sciences
(301) 594–2172
www.nigms.nih.gov

### National Institute of Mental Health
(301) 443–3673
www.nimh.nih.gov

### National Institute of Neurological Disorders and Stroke
(301) 496–9746
www.ninds.nih.gov

### National Institute of Nursing Research
(301) 496–8230
www.ninr.nih.gov/ninr

### National Library of Medicine
(301) 496–8834
www.nlm.nih.gov

### National Center for Advancing Translational Sciences (NCATS)
(301) 435-0888
ncats.nih.gov

### National Center for Complementary and Alternative Medicine
(301) 435–6826
www.nccam.nih.gov

## U.S. National Science Foundation
(703) 292-5111
www.nsf.gov

## World Health Organization
+41 22 791 2111
www.who.int

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Statistics for diseases and conditions were obtained from the Centers for Disease Control and Prevention, World Health Organization, National Institutes of Health, and voluntary organizations.

*Brain Facts* is produced as part of SfN's commitment to advance public education and information about the brain and nervous system. For more information or to download a free copy, please go to http://brainfacts.org/about-neuroscience/brain-facts-book/.

The Society gratefully acknowledges the invaluable assistance of more than 60 neuroscientists who volunteered their time, expertise, and guidance in the development and update of this book. In particular, SfN recognizes the assistance and guidance of its Public Education and Communication Committee, especially James McNamara, MD, committee chair, and the following committee members who dedicated significant time as section editors: Judy Cameron, PhD; Barry Kaplan, PhD; David Parfitt, PhD; Angela Jane Roskams, PhD; Patricia Trimmer, PhD; Gary Westbrook, MD. SfN also recognizes the important contributions of Nicholas Spitzer, PhD, inaugural editor-in-chief for *BrainFacts.org*.

Deputy Executive Director (Programs): Mona Miller

Executive Editor: Debra Speert, PhD

Contributing Editor: Todd Bentsen

Managing Editor: Marilyn Fenichel, Cassell & Fenichel, LLC

Illustrators: Lydia V. Kibiuk, Baltimore, MD; Devon Stuart, Hershey, PA
Printed and bound in the United States of America
Seventh Edition

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## FOUNDING PARTNERS


### The Gatsby Charitable Foundation

Gatsby is a Trust set up by David Sainsbury to realise his charitable objectives. We focus our support on a limited number of areas:

- Plant science research
- Neuroscience research
- Science and engineering education
- Economic development in Africa
- Public policy research and advice
- The arts

We are proactive in devising projects to achieve our aims. We are enthusiastic about supporting innovation. We are analytical as we believe it is important to understand the opportunities and problems we tackle. We take a long-term view as we do not think much can be achieved by short, one-off projects. We are always enthusiastic to form partnerships with other organisations who share our goals.


### The Kavli Foundation

The Kavli Foundation, established by Fred Kavli, is dedicated to advancing science for the benefit of humanity, promoting public understanding of scientific research, and supporting scientists and their work. The Foundation's mission is implemented through an international program of research institutes in the fields of astrophysics and theoretical physics, nanoscience, and neuroscience, and through the support of conferences, symposia, endowed professorships, journalism workshops and other activities. The Foundation is also a founding partner of the Kavli Prizes, biennial $1 million prizes that recognize scientists for their seminal advances in three research areas: astrophysics, nanoscience and neuroscience.

SOCIETY *for* NEUROSCIENCE

The Society for Neuroscience is the world's largest organization of scientists and physicians dedicated to understanding the brain, spinal cord, and peripheral nervous system.

Neuroscientists investigate the molecular and cellular levels of the nervous system; the neuronal systems responsible for sensory and motor function; and the basis of higher order processes, such as cognition and emotion. This research provides the basis for understanding the medical fields that are concerned with treating nervous system disorders. These medical specialties include neurology, neurosurgery, psychiatry, and ophthalmology.

Founded in 1969, the Society has grown from 500 charter members to more than 42,000 members worldwide. The Society has more than 150 local or regional chapters. With activities ranging from lectures to networking events and information sharing, SfN chapters enable individual members to engage their colleagues at the local level.

The mission of the Society is to:

- Advance the understanding of the brain and the nervous system by bringing together scientists of diverse backgrounds, by facilitating the integration of research directed at all levels of biological organization, and by encouraging translational research and the application of new scientific knowledge to develop improved disease treatments and cures.
- Provide professional development activities, information, and educational resources for neuroscientists at all stages of their careers, including undergraduates, graduates, and postdoctoral fellows, and increase participation of scientists from a diversity of cultural and ethnic backgrounds.
- Promote public information and general education about the nature of scientific discovery and the results and implications of the latest neuroscience research. Support active and continuing discussions on ethical issues relating to the conduct and outcomes of neuroscience research.
- Inform legislators and other policy-makers about new scientific knowledge and recent developments in neuroscience research and their implications for public policy, societal benefit, and continued scientific progress.

The exchange of scientific information occurs at an annual fall meeting where more than 16,000 reports of new scientific findings are presented and more than 30,000 people attend. This meeting, the largest of its kind in the world, is the arena for the presentation of new results in neuroscience.

The Society's weekly journal, *The Journal of Neuroscience*, contains articles spanning the entire range of neuroscience research and has subscribers worldwide. The Society's ongoing education and professional development efforts reach teachers and help promote the education of Society members. Print and electronic publications inform members about Society activities.

A major goal of the Society is to inform the public about the progress and benefits of neuroscience research. The Society accomplishes this goal by providing information about neuroscience to schoolteachers and encouraging its members to speak to young people about the human brain and nervous system.