THE 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 neural 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 1989, the Society has grown from 502 charter members to more than 38,000 members worldwide. The Society has more than 100 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 10,000 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.
IT SETS HUMANS APART from all other species by allowing us to achieve the wonders of walking on the moon and composing masterpieces of literature, art, and music. The human brain — a spongy, three-pound mass of fatty tissue — has been compared to a telephone switchboard and a supercomputer. But the brain is much more complicated than either of these devices, a fact scientists confirm almost daily, with each new discovery. The extent of the brain’s capabilities is unknown, but it is the most complex living structure known in the universe. This single organ controls body activities, ranging from heart rate and sexual function to emotion, learning, and memory. The brain is even thought to influence the immune system’s response to disease and to determine, in part, how well people respond to medical treatments. Ultimately, it shapes our thoughts, hopes, dreams, and imaginations. In short, the brain is what makes us human.

Neuroscientists have the daunting task of deciphering the mystery of this most complex of all machines: how as many as 100 billion nerve cells are produced, grow, and organize themselves into effective, functionally active systems that ordinarily remain in working order throughout a person’s lifetime. The motivation of researchers is twofold: to understand human behavior better — from how we learn to why people have trouble getting along together — and to discover ways to prevent or cure many devastating brain disorders.

The 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, at costs exceeding $460 billion. In addition, mental disorders, excluding drug and alcohol problems, strike 44 million adults a year at a cost of some $148 billion.

Since the Decade of the Brain, which ended in 2000, neuroscience has made significant discoveries in these areas:

**Genetics** Disease genes have been identified that are key to several neurodegenerative disorders, including Alzheimer’s disease, Huntington’s disease, and amyotrophic lateral sclerosis. 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 underlie the development of diseases. With the mapping of the human genome, neuroscientists have made significant discoveries in these areas:

**Gene-Environment Interactions** Most major diseases that have a genetic basis are strongly influenced by the environment. For example, identical twins have an increased risk compared with nonidentical siblings of getting the same disease; however, if one twin gets the disease, the probability that the other will also be affected is only 30 to 60 percent. Environmental influences include many factors such as toxic substances, diet, and level of physical activity but also encompass 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. These discoveries are leading to new approaches to the treatment of chronic pain.

**New Drugs** Researchers have gained insight into the mechanisms of molecular neuropharmacology, which provides a new understanding of mechanisms of addiction. These advances have led to new treatments for depression and obsessive-compulsive disorder.

**Imaging** Revolutionary imaging techniques, including magnetic resonance imaging and positron emission tomography, have revealed the brain systems underlying attention, memory, and emotions and indicate dynamic changes that occur in schizophrenia and other disorders.

**Cell Death** The discovery of how and why neurons die, as well as the discovery of stem cells, which divide and form new neurons, has many clinical applications. This has dramatically improved the outlook for 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 have been brought to clinical practice.

**Brain Development** New principles and newly discovered molecules responsible for guiding nervous system development now give scientists a better understanding of certain disorders of childhood. Together with the discovery of stem cells, these advances are paving the way for novel strategies for helping the brain or spinal cord regain functions lost as a result of injury or developmental dysfunction. Federal neuroscience research funding of more than $5 billion annually and private support will continue to expand our knowledge of the brain in the years ahead.

**The TOLL OF SELECTED BRAIN AND NERVOUS SYSTEM DISORDERS ON AMERICANS**

**Condition** | **Total Cases** | **Cost per Year (U.S. dollars)**
--- | --- | ---
Sleep Disorders | 70 million | 100 billion
Hearing Loss | 32 million | 2.5 billion
All Depressive Disorders | 20.9 million | 70 billion
Traumatic Brain Injury | 5.3 million | 60 billion
Stroke | 5.2 million | 51 billion
Alzheimer’s Disease | 5 million | 1.48 billion
Schizophrenia | 2 million | 3.25 billion
Parkinson’s Disease | 1 million | 5.6 billion
Multiple Sclerosis | 400,000 | 10.6 billion
Spinal Cord Injury | 250,000 | 10 billion
Huntington’s Disease | 30,000 | 2 billion

* Estimates provided by the Centers for Disease Control and Prevention, National Institutes of Health, and voluntary organizations.

THE TOLL OF SELECTED BRAIN AND NERVOUS SYSTEM DISORDERS ON AMERICANS

THE BRAIN: Cerebral cortex (top image). This part of the brain is divided into four sections: the occipital lobe, the temporal lobe, the parietal lobe, and the frontal lobe. Functions, such as vision, hearing, and speech, are distributed in selected regions. Some regions are associated with more than one function. Major internal structures (bottom image). The (1) forebrain is credited with the highest intellectual functions — thinking, planning, and problem-solving. The hippocampus is involved in memory. The thalamus serves as a relay station for almost all the information coming into the brain. Neurons in the hypothalamus serve as relay stations for internal regulatory systems by monitoring information coming in from the autonomic nervous system and commanding the body through these nerves and the pituitary gland. On the upper surface of the (2) midbrain are two pairs of small hills, colliculi, collections of cells that relay specific sensory information from sense organs to the brain. The (3) hindbrain consists of the pons and medulla oblongata, which help control respiration and heart rhythms, and the cerebellum, which helps control movement as well as cognitive processes that require precise timing.

THE BRAIN FACTS

**5**
THE NEURON

A SPECIALIZED CELL designed to transmit information to other nerve cells, muscle, or gland cells, the neuron is the basic working unit of the brain. The brain is what it is because of the structural and functional properties of interconnected neurons. The brain contains between 1 billion and 100 billion neurons, depending on the species.

The neuron consists of a cell body, dendrites, and an axon. The cell body contains the nucleus and cytoplasm. The electrically excitableaxon 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 and cell body are covered by synaptosomes formed by the ends of axons from other neurons.

Neurons signal by transmitting electrical impulses along their axons, which can range in length from a tiny fraction of an inch to three feet or more. Many axons are covered with a layer of myelin sheath, which speeds the transmission of electrical signals along the axon. This sheath is made of specialized cells called oligodendrocytes in the brain and Schwann cells in the peripheral nervous system.

Nerve impulses involve the opening and closing of ion channels, which 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 these 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 at one point on the cell’s membrane, when the neuron switches from an internal negative charge to a positive charge state. The change, called an action potential, then passes along the membrane of the axon at speeds up to several hundred miles per hour. In this way, a neuron may be able to fire impulses multiple times every second.

Upon reaching the end of an axon, these voltage changes trigger the release of neurotransmitters, the brain’s chemical messengers. Neurotransmitters are released at nerve terminals, diffuse across the extracellular space, 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. And when the neurotransmitter is in place, this interaction alters the target cell’s membrane potential and triggers a response, such as the generation of an action potential, contraction of a muscle, stimulation of an enzyme activity, or inhibition of neurotransmitter release from the target cell.

Increased understanding of neurotransmitters in the brain and the action of drugs on these chemicals — gained largely through animal research — guides one of the largest fields in neuroscience. Armed with this information, scientists hope to understand the circuits responsible for disorders such as Alzheimer’s disease and Parkinson’s disease. Sorting out the various chemical circuits is vital to understanding how the brain stores memories, why sex is such a powerful motivation, and what makes up the biological basis of mental illness.

Neurotransmitters and neuromodulators

Acetylcholine

The first neurotransmitter, identified about 75 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 also serves as a transmitter in many regions of the brain.

ACh is formed at the axon terminals. When an action potential arrives at the nerve terminal, the 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 opens sodium channels and causes the muscle to contract. ACh is then broken down by the enzyme acetylcholinesterase and reabsorbed in the nerve terminal. Antibodies that block one type of receptor for ACh cause myasthenia gravis, a disease characterized by fatigue and muscle weakness.

Much less is known about ACh in the brain. Recent discoveries suggest, however, 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 one goal of current research. Drugs that inhibit acetylcholinesterase 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.

Key questions remain about the NMDA receptor’s precise structure, regulation, location, and function. Developing drugs to block or stimulate activity at NMDA receptors holds promise for improving brain function and treating neurological and psychiatric disorders. catecholamines

Dopamine and norepinephrine are widely present in the brain and peripheral nervous system. Dopamine is present in three principal circuits in the brain; these circuits control movement, cause psychiatric symptoms such as psychosis, and regulate hormonal responses.

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 symptoms including muscle tremors, rigidity, and difficulty in moving. Thus, medical scientists have found that the 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.

NEURON: A neuron fires by transmitting electrical signals along its axon. When signals reach the end of the axon, they trigger the release of neurotransmitters that are stored in packets called vesicles. Neurotransmitters bind to receptor molecules on the surface of adjacent neurons. The point of virtual contact is known as the synapse.
Nerve fibers containing norepinephrine are present throughout the brain. Deficiencies in this transmitter occur in patients with Alzheimer’s disease, Parkinson’s disease, and Korsakoff’s syndrome, a cognitive disorder associated with chronic alcoholism. Thus, researchers believe norepinephrine may play a role in both learning and memory. Norepinephrine is also secreted by the sympathetic nervous system in the periphery to regulate heart rate and blood pressure. Acute stress increases the release of norepinephrine from sympathetic nerves and the adrenal medulla.

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 implicated in sleep, mood, depression, and anxiety. Because serotonin controls the 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 disorders.

Peptides These are chains of amino acids linked together. Peptides differ from proteins, which are much larger and have more complex combinations of amino acids.

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 produced by the brain that resembles morphine, an opium derivative used medically to kill pain. They named it enkephalin, literally meaning “in the head.” Soon after, other types of opioid peptides, endorphins, were discovered. Endorphins, whose name comes from endogenous morphine, act like opium or morphine to kill pain or cause sleepiness.

The precise role of the naturally occurring opioid peptides is unclear. A simplistic hypothesis is that they are released by brain neurons in times of stress to minimize pain and enhance adaptive behavior. The presence of opioid peptides may explain, for example, why injuries received during the stress of combat are often not remembered, 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 glucose release, as occurs in stroke, neuronal damage following the stroke may be attributable in part to nitric oxide.

Second messengers Substances that trigger biochemical communication within cells, after the action of neurotransmitters at their receptors, are called second messengers; these intracellular effects may be responsible for long-term changes in the nervous system. They 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 years.

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 adenyl cyclase to convert ATP to cyclic adenosine monophosphate (cAMP). The second messenger, 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, rather than acting as a messenger between one neuron and another.

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 cerebellum — the largest part of the brain, consisting of two hemispheres — as well as the processes of growth and development. In addition, direct effects of second messengers on the genetic material of cells may lead to long-term alterations in cellular functioning and ultimately in behavior.
**THE CELLS OF THE NERVOUS SYSTEM**

connect with one another in trillions of remarkably specific patterns that form and change over the course of an organism’s life. These connections develop among various types of neurons, a process that begins in the embryos. First, appropriate types of neurons must arise in appropriate numbers and migrate to appropriate places. The axons and dendrites that form the connections then extend from these nerve cells, and the growth of axons must be guided over long distances to reach the appropriate targets. Axons must recognize specific target cells. The connections that form initially then mature, with the activity and experience of early postnatal life playing a key role in their refinement. The degree of complexity in the brain, and therefore the amount of interaction required to regulate its development, is far greater than in other organs of the body. Scientists studying development are working to reveal how these complicated processes of connecting and reshaping occur.

Many initial steps in brain development are similar across species, although later steps are different. By studying these similarities and differences, scientists can learn about normal human brain development and can learn how brain abnormalities, such as mental retardation and other disorders, can be prevented or treated.

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 development and can learn how brain abnormalities, such as mental retardation and other disorders, can be prevented or treated.

Birth of neurons and brain wiring

Three to four weeks after conception, one of the two cell layers of the gelatinlike human embryo, about one-tenth of an inch long, starts to thicken and build up along the middle. As the cells continue to divide and this flat neural plate grows, parallel ridges, similar to the creases in a paper airplane, rise across its surface. Within a few days, the ridges fold in toward each other and form to make the hollow neural tube. The top of the tube thickens into three bulges that form the hindbrain, midbrain, and forebrain. The first signs of the eyes and the hemispheres of the brain appear later in development.

The embryo has three layers that undergo many interactions in order to grow into organs, bone, muscle, skin, or neural tissue. Skin and neural tissue arise from one layer, the ectoderm, in response to signals provided by the adjacent layer, the mesoderm. A number of molecules interact to determine whether the ectoderm becomes neural tissue or develops in another way to become skin. Studies of spinal cord development in frogs show that one major mechanism depends on specific proteins that inhibit the activity of other proteins. In areas where no inhibition occurs, the tissue becomes skin. In areas where proteins secreted from the mesoderm do lead to inhibition, the tissue becomes neural.

Once the ectodermal tissue has acquired its neural fate, more signaling interactions determine which type of brain cell forms. The mature nervous system contains a vast array of cell types, which can be divided into two main categories: the neurons, responsible primarily for signaling, and supporting cells called glial cells.

Researchers are finding that the destiny of neural tissue depends on a number of elements, including cell position within the nervous system, that define the environmental signals to which the cells are exposed. For example, a key factor in spinal cord development is a secreted protein called sonic hedgehog that is similar to a signaling protein found in flies. The protein, initially secreted from mesodermal tissue lying beneath the developing spinal cord, marks directly adjacent neural cells to become a specialized class of glial cells. Cells farther away are exposed to lower concentrations of sonic hedgehog, and 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.

A combination of signals also determines the type of chemical messages, or 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 a matter of choice. Scientists found that when certain neurons are maintained in a dish with no other cell types, they produce the neurotransmitter norepinephrine. In contrast, if the same neurons are maintained in a dish with another cell type, they produce the neurotransmitter acetylcholine. Some neurons have the genes required to produce these molecules, but the type of neurotransmitter is determined by environmental factors.

The diagram shows that the brain develops from the embryonic forebrain, midbrain, and hindbrain. The structures that develop from these regions are shown in the diagram. The forebrain develops into the telencephalon, which forms the cerebral cortex, and the diencephalon, which includes the thalamus and hypothalamus. The midbrain develops into the midbrain, which contains the substantia nigra and red nucleus. The hindbrain develops into the pons and medulla oblongata. The spinal cord develops from the notochord and the somites, which are blocks of mesoderm that form the muscle layers of the body. The somites also give rise to the neural crest, which gives rise to the peripheral nervous system. The diagram shows the development of the brain and nervous system over time, with the different stages shown in different colors.

**BRAIN DEVELOPMENT**

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). Irregular ridges, or convolutions, are clearly seen by six months. Neuroscience researchers are working to reveal how these complicated processes of connecting and reshaping occur. Many initial steps in brain development are similar across species, although later steps are different. By studying these similarities and differences, scientists can learn about normal human brain development and can learn how brain abnormalities, such as mental retardation and other disorders, can be prevented or treated. 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 development and can learn how brain abnormalities, such as mental retardation and other disorders, can be prevented or treated. Birth of neurons and brain wiring

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**NEURON MIGRATION**

A cross-sectional view of the occipital lobe (which processes visual information) of a three-month-old monkey fetus brain (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. In vivo, it needs adhesion molecules, which recognize the pathway, and contractile proteins to propel it along.
Neurons are initially produced along the central canal in the neural tube. These neurons then migrate from their birthplace to a final destination in the brain. They collect together to form each of the various brain structures and acquire specific ways of transmitting nerve messages. Their axons grow long distances to find and connect with appropriate partners, forming elaborate and specific circuits. Finally, sculpting action eliminates redundant or improper connections, honing the specific purposes of the circuits that remain. The result is a precisely elaborated adult network of 100 billion neurons capable of body movement, perception, emotion, and thought.

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 migration of neurons occurs in most structures of the brain but is particularly prominent in the formation of a large cerebral cortex in primates, including humans. In this structure, neurons slither from the place of origin near the ventricular surface, along non-neuronal fibers that form a trail, to their proper destination. Proper neuron migration requires multiple mechanisms, including the recognition of the proper path and the ability to move long distances. One mechanism for long-distance migration is the movement of neurons along elongated fibers that form transient scaffolding in the fetal brain. In another mode, inhibitory interneurons migrate tangentially across the brain. Many external forces, such as alcohol, cocaine, or radiation, prevent proper neuronal migration and result 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.

Once the neurons reach their final location, they must make the proper connections for a particular function to occur; for example, vision or hearing. They do this through their axons. These thin appendages can stretch out a thousand times longer than the cell body from which they arise. The journey of most axons ends when they thicken appendages, called dendrites, on other neurons. These target neurons can be located at a considerable distance, sometimes at the opposite side of the brain. In the case of a motor neuron, the axon may travel from the spinal cord all the way down to a foot muscle.

Axon growth is directed by growth cones. These enlargements of the axon tip actively explore the environment as they seek out precise destinations. 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 15 semaphorins and at least 10 ephrins.

Perhaps the most remarkable finding is that most of these proteins are common to worms, insects, and mammals, including humans. Each family protein is smaller in flies or worms than in mice or people, but its functions are quite similar. It has therefore been possible to use such animals 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 found in worms and proved invaluable in finding the corresponding and related, human receptors.

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Once axons reach their targets, they form synapses, which permit electric signals in the axon to jump to the next cell, 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, whereby the axon chooses the proper neuron, and often the proper part of the target, once it arrives at its destination. Several of these recognition molecules have been identified in the past few years.

Researchers also have had success identifying the 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 contact and receiving cells to ensure that the contact is formed properly and that the sending and receiving specializations are precisely matched. 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 of these molecules are now thought to confer susceptibility to disorders such as autism, and the loss of others may underlie the degradation of synapses that occurs during aging.

Many axons in the brain require a sheath of myelin to enhance the speed of conduction. The process of wrapping axons in myelin occurs last and can take years to complete in some areas of the brain.

Parasympathetic nervous system, which conserves energy and resources during times of stress and arousal, and the parasympathetic nervous system, which conserves energy and resources during relaxed states.

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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 directly by the damage they inflict 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 too many 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 than and twice as dense as those in an adult primate. Communications...
Research also shows that enriched environments can bolster brain development. For example, studies show that animals brought up in toy-filled surroundings have more branches on their neurons and more connections than isolated animals. In one recent study, scientists found that enriched environments resulted in more neurons in a brain area involved in memory.

Many people have observed that children can learn languages with greater proficiency than adults, and recent research suggests that the heightened activity of the critical period may contribute to this robust learning. Interestingly, compared with adults, children have an increased incidence of certain disorders that involve excessive brain activity, such as epilepsy. Many epilepsy syndromes appear during childhood and fade away by adulthood. Brain development in people continues into the early 20s — even the brain of an adolescent is not completely mature. One of the later aspects of brain development is the completion of myelination of the axons connecting one brain area to another. This process starts around birth and moves from the back of the brain to the front: The frontal lobes are the last to become “connected” with fast-conducting myelinated axons. Major functions of the frontal lobes are judgment, insight, and impulse control, and so the acquisition of these attributes becomes the last step in the creation of an adult human brain.

Scientists hope that new insight into brain development will lead to treatments for those with learning disabilities, brain damage, and neurodegenerative disorders and will help us understand aging.

**Critical periods**

Although most of the neuronal cell death occurs in the embryo, the pruning down of connections occurs in large part during critical periods in early postnatal life. These are windows of time during development when the nervous system must obtain certain critical experiences, such as sensory, movement, or emotional input, to develop properly. These periods are characterized by high learning rates.

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. Injury or deprivation, either sensory or social, occurring at a certain stage of postnatal life may affect one aspect of development, whereas the same injury at a different period may affect another aspect.

In one example, if a monkey is reared from birth to 6 months of age with one eyelid closed, the animal permanently loses 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 “crossed eyes” in children.

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Although the process is not yet completely understood, recent findings 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. These findings of separate processing systems come from anatomical and physiological studies in monkeys. They are supported by human psychological studies showing 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.

Why movement and depth perception should be emphasized by one processing system may be explained by a school of thought called Gestalt psychology. 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? This involves extracting biologically relevant information at each stage and associating firing patterns of neuronal populations with past experience.

Vision studies also have led to better treatment for visual disorders. Information from research in cats and monkeys has improved the therapy for strabismus, or squint, a term for 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 6 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 or prescribing exercises or an eye patch. Now strabismus is corrected very early in life — before age 4, when normal vision can still be restored.

Hearing

Often considered the most important sense for humans, hearing allows us to communicate with each other by receiving sounds and interpreting speech. It also gives us information vital to survival; for instance, by alerting us to an approaching car.

Like the visual system, our hearing system distinguishes several qualities in the signals it detects. Our hearing system, however, HEARING. From the chirping of crickets to the roar of a rocket engine, sound waves are collected by the external ear — the pinna and the external auditory canal — and funnel 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 vibration on to the stapes (stirrup). The stapes pushes on the oval window, which separates the air-filled middle ear from the fluid-filled inner ear, to produce pressure waves in the snail-shaped cochlea of the inner ear. Hair cells in the cochlea, riding on the vibrating basilar membrane, have “hair bundles” of microscopic stereocilia that are deflected by the overlying tectorial membrane. Hair cells convert the mechanical vibration to an electrical signal; they, in turn, release chemicals to excite the 30,000 fibers of the auditory nerve that carry the signals to the brainstem. Auditory information is analyzed by multiple brain centers as it flows to the temporal gyrus or auditory cortex, the part of the brain involved in perceiving sound.
does not blend different sounds, as the visual system does when two 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.

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Hair cells in the cochlea, riding on the basilar membrane, have hair bundles of microscopic hairlike stereocilia that are deflected by the overlying tectorial membrane. Hair cells convert the mechanical vibration to an electrical signal; they in turn excite the 30,000 fibers of the auditory nerve that carry the signals to the brainstem. Because each hair cell rides on a different part of the basilar membrane, each is best excited by a different frequency, and so 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 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 like a flute, and some to complex sounds like a violin. Some respond to pure tones of similar frequency. However, they specialize in different regions to vibrate.

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prisingly, acuity is greatest in the most densely nerve-packed areas of the body. The threshold is lowest on the fingers and lips.

Until recently, pain was thought to represent a simple message resulting from neurons sending electrical impulses from a site of injury directly to the brain. We now know that the process is far more complicated. Nerve impulses from sites of injury can persist for hours, days, or longer. Moreover, 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 even when the injury is no longer present.

The sensory fibers that respond to stimuli that damage tissue and can cause pain are called nociceptors. Different nociceptor subsets express molecules that are responsible for the response to noxious (i.e., painful) mechanical, thermal, or chemical stimulation. Interestingly, these same molecules respond to plant-derived chemicals that can produce pain, such as capsaicin, garlic, and wasabi. Tissue injury also causes the release of numerous chemicals at the site of damage and inflammation. For example, 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 normally innocuous stimuli can produce pain (as with sunburned skin).

Pain messages are transmitted to the spinal cord via small myelinated fibers and very small unmyelinated fibers. The small, myelinated, pain-sensitive nerve fibers 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, which is involved in the process by which pain messages become a conscious experience. The experience of pain is not just a function of the magnitude of the injury or even the intensity of the impulse activity generated by the injury. The setting in which the injury occurs (e.g., the pain of childbirth or that produced in a car accident) and the emotional component of the experience are also major contributors to the overall 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. The endorphins act at multiple opioid receptors in the brain and spinal cord, a discovery that has had important implications for pain therapy. For example, scientists began studying the spinal delivery of opioids when they discovered a dense distribution of opioid receptors in the spinal cord horn. Such treatments were begun in humans after the method was successfully used in animals; the technique is now common in treating pain after surgery.

Modern imaging tools are now used to monitor brain activity 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. The stimulus is still experienced, but it doesn’t hurt anymore. As such techniques for brain study improve, it should be possible to better monitor the changes in the brain that occur in people with persistent pain and to better evaluate the different pain-killing drugs being developed.
LEARNING AND MEMORY. A major break-through 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 and intractable epilepsy, and an experimental surgical treatment involving removal of the medial regions of his temporal lobes greatly alleviated the seizures. However, the surgery left H.M. with severe amnesia. He can remember recent events for only a few minutes and is unable to form explicit memories of new experiences. Talk with him awhile, and then leave the room. When you return, he has no recollection of ever having seen you.

Despite his inability to remember new information, H.M. remembers his childhood very well. From these observations, researchers concluded that the parts of H.M.'s medial temporal lobe that were removed, including the hippocampus and parahippocampal region, play critical roles in converting memories of experiences from short-term memories to long-term, permanent memories. The fact that H.M. retains some memories for events that occurred long before his surgery indicates that the medial temporal region is not the site of permanent storage but instead plays a role in the organization and permanent storage of memories elsewhere in the brain.

The medial temporal region is richly 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, cortical areas are important for the long-term storage of knowledge about facts and events and for how this knowledge is used in everyday situations.

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 to support declarative memory. These cortical areas play a distinct role in complex aspects of perception, movement, emotion, and cognition.

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.

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 those functions, the prefrontal cortex also interacts with a large network of posterior cortical areas that encode, maintain, and retrieve specific types of information, such as visual images, sounds, and words, as well as where important events occurred and much more.

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 happened at a particular place and time are called episodic memories. It is generally believed that the medial temporal lobe areas serve a critical role in the initial processing and storage of these memories.

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, 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 are time-dependent.

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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 occurs through 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 entry of calcium ions into the synapse, which activates the cyclic adenosine monophosphate (cAMP) molecule. This molecule 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 activate growth of the synapse and increase 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, and 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. It 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 the neural basis of language is not fully understood, scientists have learned a great deal about this function of the brain from studies of patients who have lost speech and language abilities owing to stroke, and from brain imaging studies of normal people.

It has long been known that damage to different regions within the left hemisphere produces different kinds of language disorders, or aphasia. Damage to the left frontal lobe can produce nonfluent aphasia, 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. By comparison, comprehension of heard speech is spared, 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 muddled with errors in sound and word selection and tends to be ungrammatical 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 aphasic’s speech can often comprehend bits and pieces of a spoken utterance and can comprehend 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.

Recently, functional imaging methods have identified new structures involved in language. For example, 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 translate between speech recognition and speech production systems. This circuit is involved in speech development and is thought to support verbal short-term memory.

Although the understanding of how language is implemented in the brain is far from complete, there are now several techniques that may be used to gain important insights into this critical aspect of brain function.

Movement

FROM THE STANDS, 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. This is made possible by a finely tuned and highly complex central nervous system, which controls the actions of hundreds of muscles. Through learning, the nervous system can adapt to changing movement requirements to accomplish everyday marvels and to perform them more skillfully with practice.

To understand how the nervous system performs such tricks, we have to start with the muscles, for these are 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, so they are called skeletal muscles. Activation of a given muscle can open or close the joints that it spans, depending upon whether it is a flexor (closer) or extensor (opener).

In addition, if flexors and extensors at the same joint are activated together, they can “stiffen” a joint, thus maintaining limb position in the face of unpredictable external forces that would otherwise displace the limb. 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 placing the joint or limb at a desired position.

Some muscles act on soft tissue, such as the muscles that move the eyes and tongue and those that control facial expression. These muscles also are under control of the central nervous system, and their principles of operation are similar to those that attach to bone.

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. On the other hand, 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 innervates are called a functional unit referred to as a motor unit. These motor units are the critical link between the brain and muscles. If the motor neurons die, which can happen in certain diseases, a person is no longer able to move, either voluntarily or through reflexes.

Perhaps the simplest and most fundamental movements are reflexes. These are relatively fixed, automatic muscle responses to particular stimuli, such as the sudden withdrawal of the foot when you step on a sharp object or the slight extension of the leg when a physician taps your 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 knee movement referred to above is produced by a slight stretch of the knee exterior 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. Inactivated 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 in reflex control of the joint at which the muscle acts and also for control of voluntary 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 antagonistic 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 more amazing, the nature of the feedback that it receives from sensory receptors in the muscles as movements occur. For example, the sensitivity of the muscle spindle organs is controlled 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.

In addition to such exquisite sensing and control of muscle length by muscle spindles, 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. We now know that these complex systems are coordinated and organized to respond differently for tasks that require precise control of position, such as holding a full teaspoon, than for those requiring rapid, strong movement, such as throwing a ball. You can experience such changes in motor strategy when you compare walking down an illuminated staircase with the same task done in the dark.

Another useful reflex is the flexion withdrawal that occurs if your bare foot encounters a sharp object. Your leg is immediately
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.

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.

Disruption of the basal ganglia can lead to serious movement disorders. For example, the depletion of the neurotransmitter dopamine from specific portions of the basal ganglia results in the tremor, rigidity, and akinesis of Parkinson’s disease. Dopamine is supplied to the basal ganglia by the axons of neurons located in the substantia nigra, a midbrain cell group. Dopamine is depleted during Parkinson’s disease because of the degeneration of the nigral neurons.

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 receives direct and powerful 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.

MOVEMENT. 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 and activates motor neurons to the stretched muscle to cause contraction (stretch reflex). The same sensory stimulus causes inactivation, or inhibition, of the motor neurons to the antagonistic muscles through connection neurons, called inhibitory neurons, within the spinal cord. Efferent nerves carry messages from sensory organs to the spinal cord; efferent nerves carry motor commands from the spinal cord to muscles. Flexion withdrawal (bottom) can occur 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 in order to maintain your balance. The latter event is called the crossed extension reflex. These responses occur very rapidly and without your attention because they are built into systems of neurons located within the spinal cord itself.
**Sleep**

Sleep remains one of the great mysteries of modern neuroscience. We spend nearly one-third of our lives asleep, but the function of sleep is still not known. Fortunately, over the past few years, researchers have made great headway in understanding some of the brain circuitry that controls wake-sleep states.

Scientists now recognize that sleep consists of several different stages; that the choreography of a night’s sleep involves the interplay of these stages, a process that depends upon a complex switching mechanism; and that the sleep stages are accompanied by daily rhythms in hormones, body temperature, and other functions.

Sleep is crucial for concentration, memory, and coordination. Without enough sleep, people have trouble focusing and responding quickly — in fact, sleep loss can have as big an effect on performance as drinking alcohol. It is also important for our emotional health. And growing evidence suggests that a lack of sleep increases the risk of a host of diseases, including diabetes, cardiovascular disease and heart attacks, stroke, depression, high blood pressure, obesity, and infections.

Disorders of sleep 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 $100 billion annually in lost productivity, medical bills, and industrial accidents. 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 to produce its various stages.

The stages of sleep were discovered in the 1950s in experiments using electroencephalography (EEG) to examine human brain waves during sleep. Researchers also measured movements of the eyes and the limbs. They found that over the course of the first hour or so of sleep each night, the brain progresses through a series of stages during which the 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 at this time, most people recall only fragmented thoughts, not an active dream.

Over the next half hour or so, brain activity alters drastically from deep slow wave sleep to generate neocortical EEG waves that are 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). This state is often called rapid eye movement (REM) sleep. During REM sleep, there is active dreaming. Heart rate, blood pressure, and body temperature become much more variable. Men often have erections during this stage of sleep. 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, often complaining 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 people have difficulty falling asleep initially, but other people fall asleep 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 with a sense of completeness. People will report that they feel rested and refreshed after such sleep, but in fact, they sleep less than the recommended amount.

Other people have episodes in which their memories are intermittent jerks of the legs or arms that occur as the individual enters slow wave sleep and can cause a sensation of tugging or pulling. These movements are called leg movements during sleep (LMS). LMS can be triggered by emotional experiences, even by hearing a funny joke.

Recently, studies into the mechanism of narcolepsy have given researchers major insight into the processes that control these mysterious transitions between waking, slow wave sleep, and REM sleep states.

**How is sleep regulated?**

During wakefulness, the brain is kept in an active or aroused state by the actions of two major systems of nerve cells that use either acetylcholine or monoamines, such as noradrenaline, serotonin, dopamine, and histamine, as their neurotransmitters. Nerve cells in the upper part of the brainstem send inputs to the thalamus, where they lose muscle tone — similar to what occurs during REM sleep but while they are awake. These attacks of paralysis, known as cataplexy, can be triggered by emotional experiences, even by hearing a funny joke.

During REM sleep, the cholinergic nerve cells activate the thalamus, producing an EEG pattern that is similar to wakefulness, causing arousal from sleep. Other people have episodes in which their muscles fail to become paralyzed during REM sleep, and they act out their dreams. This REM behavior disorder also 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 2,500 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 containing the neurotransmitter orexin (also known as hypocretin). Narcoleptics have sleep attacks during the day, in which they suddenly fall asleep. This is socially disruptive, as well as dangerous — for example, if they strike while they are driving. They tend to enter REM sleep very quickly 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 — similar to what occurs during REM sleep but while they are awake. These attacks of paralysis, known as cataplexy, can be triggered by emotional experiences, even by hearing a funny joke.

Recent studies into the mechanism of narcolepsy have given researchers major insight into the processes that control these mysterious transitions between waking, slow wave sleep, and REM sleep states.

**Sleep patterns**

During a night of sleep, the brain waves of a young adult recorded by the electroencephalogram (EEG) gradually slow down and become larger as the individual passes into deeper stages of slow wave sleep. After about an hour, the brain re-emerges through the same series of stages, and there is usually a brief period of REM sleep (an area dark area of graph), during which the EEG is similar to wakefulness. The body is completely relaxed; the person is deeply unconscious and usually is dreaming. The cycle repeats over the course of the night, with more REM sleep, and less time spent in the deeper stages of slow wave sleep as the night progresses.

**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 to produce its various stages.

The stages of sleep were discovered in the 1950s in experiments using electroencephalography (EEG) to examine human brain waves during sleep. Researchers also measured movements of the eyes and the limbs. They found that over the course of the first hour or so of sleep each night, the brain progresses through a series of stages during which the 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 at this time, most people recall only fragmented thoughts, not an active dream.

Over the next half hour or so, brain activity alters drastically from deep slow wave sleep to generate neocortical EEG waves that are 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). This state is often called rapid eye movement (REM) sleep. During REM sleep, there is active dreaming. Heart rate, blood pressure, and body temperature become much more variable. Men often have erections during this stage of sleep. 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, often complaining 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 people have difficulty falling asleep initially, but other people fall asleep 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 with a sense of completeness. People will report that they feel rested and refreshed after such sleep, but in fact, they sleep less than the recommended amount.

Other people have episodes in which their memories are intermittent jerks of the legs or arms that occur as the individual enters slow wave sleep and can cause a sensation of tugging or pulling. These movements are called leg movements during sleep (LMS). LMS can be triggered by emotional experiences, even by hearing a funny joke.

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The waking and sleeping brain. Wakefulness is maintained by activity in two systems of neurons. Neurons that make the neurotransmitter acetylcholine are located in two main arousal centers, one in the brainstem (green pathways) and one in the forebrain (red pathway). The brainstem arousal center supplies the acetylcholine for the thalamus and brainstem, and the forebrain arousal center supplies that for the cerebral cortex. Activation of these centers alone can create rapid eye movement sleep. Activation of other neurons that make monoamine neurotransmitters such as norepinephrine, serotonin, and histamine (blue pathways) is needed for waking.

But the monoamine pathway from the upper brainstem directly to the cerebral cortex is quiet. As a result, the input from the thalamus to the cerebral cortex is perceived as dreams. When the nerve cells containing the monoamine neurotransmitters are active, they suppress the occurrence of REM sleep.

The brainstem cell groups that control arousal from sleep are, in turn, influenced by two groups of nerve cells in the hypothalamus, the part of the brain that controls basic body cycles. One group of nerve cells, in the ventrolateral preoptic nucleus, contains the inhibitory neurotransmitters galanin and DABA. When the ventrolateral preoptic neurons fire, they are thought to turn off the arousal systems, causing sleep. Damage to the ventrolateral preoptic nucleus produces irreversible insomnia.

A second group of nerve cells in the lateral hypothalamus promotes wakefulness and suppresses REM sleep. They contain the neurotransmitter orexin, which provides an excitatory signal to the arousal system, particularly to the monoamine neurons. In experiments in which the gene for the neurotransmitter orexin was experimentally removed in mice, the animals became narcoleptic. Similarly, in two dog species with naturally occurring narcolepsy, an abnormal will sleep much more, to “repay” the debt. The slow wave sleep debt is usually “paid off” first.

The other major influence on sleep cycles is the brain’s circadian timing system. The suprachiasmatic nucleus is 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 of about 24 hours, setting the pace for daily cycles of activity, sleep, hormone release, and other bodily functions. 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. 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 in turn contacts the ventrolateral preoptic nucleus and the orexin neurons that directly regulate sleep and arousal.

Stress

The ability to react. In response to threatening events has been with us since the time of our ancient ancestors. In response to impending danger, muscles are primed, attention is focused, and nerves are ready for action — “fight or flight.” In today’s complex and fast-paced world, stressors are more consistently psychological or socially based, and we face them with less reperie. The continued stimulation of the systems that respond to threat or danger may contribute to heart disease, obesity, arthritis, and depression, as well as accelerating the aging process.

Nearly two-thirds of ailments seen in doctors’ offices are adversely affected by stress; indeed, stress can both cause diseases and exacerbate existing ones. Surveys indicate that 60 percent of Americans feel they are under a great deal of stress at least once a week. Costs due to stress from absenteeism, medical expenses, and lost productivity are estimated at $300 billion annually.

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. Among the most powerful stressors are psychological and psychosocial stressors that exist between members of the same species. Lack of control is a particularly important feature of severe psychological stress that can have physiological consequences. Most harmful are the chronic aspects of stress.

During the past several decades, researchers have found that stress both helps and harms the body. 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 to 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 can badly 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 his or her internal physiological response. Thus, by controlling your perception of events, you can do much to avoid the harmful consequences of the sorts of mild to moderate stressors that typically affect modern humans.

The immediate response. A stressful situation activates three major communication systems in the brain that regulate bodily functions. Scientists have come 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 you to run from the beach as quickly as possible.

The second communication system is the autonomic nervous system. It combines the sympathetic branch and the parasympathetic branch. The sympathetic nervous system gets us moving in emergencies, while the parasympathetic nervous system keeps the body’s maintenance systems, such as digestion, in order and calms the body’s responses to the emergency branch.

Each of these systems has a specific task. 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, and supply to the muscles increases. In contrast, the parasympathetic branch helps to regulate bodily functions and soothes the body once the stressor has passed, preventing the body from having to remain in a state of mobilization. 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 major stress hormones are epinephrine (also known as adrenaline) and cortisol. When the body is exposed to stressors, epinephrine, which combines elements of hormones and neurotransmitters, is quickly released into the bloodstream to put the body into a general state of arousal and enable it to cope with a challenge. The adrenal glands secrete glucocorticoids, which are 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. In primates, the main glucocorticoid is cortisol (hydrocortisone), whereas in rodents, it is corticosterone. Some of the actions of glucocorticoids help to mediate the stress response, while some of the 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. Cortisol promotes energy replenishment and efficient cardiovascular function.

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 acts as a wake-up signal and helps turn on appetite and physical activity. This effect of glucocorticoids may help to 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 memory of threatening situations and events, increases 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. In fact, they are an integral part of daily life and the adaptation to environmental change. The adrenal glands help protect us from stress and are essential for survival.

Chronic stress

When glucocorticoids or epinephrine are secreted in response to the prolonged psychological stress commonly encountered by modern humans, the results are not ideal. Normally, bodily systems gear up under stress and release hormones to improve memory, increase immune function, enhance muscular activity, and restore homeostasis. If you are not fighting or fleeing but standing frustrated and angry during a long-distance car trip, you are not engaging in muscular exercise. Yet these systems continue to be stimulated, and when they are stimulated chronically, the consequences are different. Memory is impaired, immune function is suppressed, and energy is stored as fat.

Overexposure to cortisol also can lead to weakened muscles and can chip away at the mechanisms that keep our body systems in a healthy balance. Elevated epinephrine release increases blood pressure. Together, elevated cortisol and epinephrine can contribute to chronic hypertension (high blood pressure), abdominal obesity, and atherosclerosis (hardening of the arteries). Epinephrine also increases the activity of body chemicals that contribute to inflammation, and these chemicals add to the burden of chronic stress, potentially leading to arthritis and possibly aging of the brain.

Stress also can contribute to sleep loss. Elevated levels of glucocorticoids can delay the onset of sleep, and sleep deprivation raises glucocorticoid levels, setting off a vicious cycle.

Scientists have identified a variety of stress-related disorders, including colitis, high blood pressure, clogged arteries, impotence and loss of sex drive in males, irregular menstrual cycles in females, and adult-onset diabetes. Aging rats show impairment of neuronal function in the hippocampus—an area of the brain important for learning, memory, and emotion—as a result of glucocorticoid secretion throughout their lifetimes.

Overexposure to glucocorticoids also increases the number of neurons damaged by stroke. Moreover, prolonged exposure before or immediately after birth can cause a decrease in the normal number of brain neurons and smaller brain size.

The immune system, which receives messages from the nervous system, also is sensitive to many of the circulating hormones of the body, including stress hormones. Although acute elevations of stress hormones actually facilitate immune function, sustained exposure to moderate to high levels of glucocorticoids acts to suppress immune function.

While acute, stress-induced immunoenhancement can be protective against disease pathogens, glucocorticoid-induced immunosuppression also can be beneficial. Normally, the glucocorticoids help reverse the immunoenhancement brought about by stress. Without this reversal, there is an increased chance of diseases of overactive immunity and inflammation, such as autoimmune disorders, which occur when the body’s immune defenses turn against body tissue. Synthetic glucocorticoids like hydrocortisone and prednisone suppress the immune system and therefore are used often to treat autoimmune and inflammatory diseases.

One important determinant of resistance or susceptibility to disease may be a person’s sense of control as opposed to a feeling of helplessness. This phenomenon may help explain large individual variations in response to disease. Scientists are trying to identify how the perception of control or helplessness influences physiological responses to stress, including the regulation of immune function.

The cardiovascular system receives many messages from the autonomic nervous system, and stressful experiences have an immediate and direct effect on heart rate and blood pressure. In the short run, these changes help in 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.

Behavioral type affects a person’s susceptibility to heart attack. People at greatest risk are hostile, irritable by trivial things, and exhibit signs of struggle against time and other challenges. Researchers found that two groups of men—one with high hostility scores and the other with low hostility scores—exhibited similar increases in blood pressure and muscle blood flow when performing a lab test. This finding confirmed that hostility scores do not predict the biological response to simple mental tasks. Then the researchers added harassment to the test by leading the subjects to believe that their performances were being unfairly criticized. Men with high hostility scores showed much larger increases in levels of stress hormones. Scientists found that harassed men with high hostility scores had larger increases in levels of stress hormones. Thus, if you have personality traits of hostility, learning to reduce or avoid anger could be important to avoid cardiovascular damage.
NEUROSCIENTISTS BELIEVE that the brain can remain relatively healthy and fully functioning as it ages and that diseases cause the most severe decline in memory, intelligence, verbal fluency, and other tasks. Researchers are investigating both the abnormal and normal 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. Almost everyone gets a bit forgetful in old age, particularly in forming memories of recent events. For example, once you reach your 20s, you may start to forget names, phone numbers, or where you parked your car, or you might respond more slowly to conflicting information. This is not disease. Some individuals, however, develop senile dementia, the progressive and severe impairment in mental function that interferes with daily living. The senile dementia include Alzheimer’s and cerebrovascular diseases and affect about 1 percent of people younger than age 65, with the incidence possibly increasing to nearly 50 percent in those older than 85. In a small, third group, mental functioning seems relatively unaffected by age. Many people do well throughout life and continue to do well even when old, at least until shortly before death. The wisdom and experience of older people often make up for deficits in performance. The oldest human, Jeanne Calment, kept her wits throughout her 122-year life span.

The belief that pronounced and progressive mental decline is inevitable was and still is popular for several reasons. For one, until the 20th century, few people lived past 65. In 1900, when average life expectancy was about 47 years, 3 million people, or 4 percent of the population, were older than age 65 and typically were ill. In 2003, when life expectancy was more than 77 years, nearly 36 million people, or more than 12 percent of the population, were older than age 65. A generation ago, frailty was seen among people in their 60s today it is more typical among those in their 80s. Moreover, few people challenged the notion that aging meant inevitable brain decline because scientists knew little about the brain or the aging process. Today’s understanding of how the normal brain ages comes from studies of the nervous system that began decades ago and are just now bearing results. Modern technologies now make it possible to explore the structure and function of the brain in more depth than ever before and to ask questions about what actually happens in its aging cells.

Thus, neuroscientists are increasingly able to distinguish between the processes of normal aging and disease. Although some changes do occur in normal aging, they are not as severe as scientists once thought and certainly do not include widespread cell loss. All human behavior is determined by how well the brain’s communication systems work. Often a failure in the cascade of one of these systems results in a disturbance of normal function. Such a failure may be caused by an abnormal biochemical process or a loss of connections between neurons.

The cause of normal brain aging remains a mystery. Dozens of theories abound. One says that specific “aging genes” are switched on at a certain time of life. Another points to genetic mutations or deletions. Other theories implicate hormonal influences, an immune system gone awry, and the accumulation of damage caused by free radicals, cell byproducts that destroy fats and proteins vital to normal cell function.

Aging neurons

The brain reaches its maximum weight near age 20; subtle changes in the chemistry and structure of the brain begin at middle life 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 as occurs in Alzheimer’s disease or after a stroke. Brain tissue can respond to damage or loss of neurons by expanding dendrites and fine-tuning connections between older neurons. A damaged brain neuron can readjust to damage only if its cell body remains intact. If it does, regrowth can occur in dendrites and axons. When neurons are destroyed, nearby surviving neurons can compensate, in part, by growing new dendrites and connections. Physical exercise also can improve neuronal functions at later ages.

Intelectual capacity

From the first large studies to monitor the same group of healthy humans for 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 uses 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 in which only minor brain abnormalities can be detected, certain spatial tasks, such as navigating to find food, tend to become more difficult with age.

The aging brain is only as resilient as its circuitry. Scientists debate whether this circuitry is changed only by neuron atrophy or whether some neuron loss over time also 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 in older people to accomplish performance levels similar to those of younger adults.

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 and 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 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 brain cells in rats given acrobatic training had more synapses per cell than rats given only physical exercise or rats that were inactive. The scientists concluded that motor learning generates new synapses. Physical exercise, however, improved blood circulation in the brain. Aerobic exercise can also improve cognitive performance in humans.

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? Is 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 speculate that certain genes may be linked to events leading to cell death in the nervous system. By understand- ing the biology of the proteins produced by genes, scientists hope to be able to influence the survival and function of neurons.
Addiction

Drug abuse is one of the nation’s most serious health problems. Indeed, 9 percent of Americans, more than 22 million people, abuse drugs on a regular basis. Recent estimates show that the abuse of drugs, including alcohol and nicotine, costs the nation more than $276 billion each year.

If continued long enough, drug abuse — often defined as harmful drug use — 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, and 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, one of which is 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 to 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 and therefore can also promote 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, whereas 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 brains of susceptible individuals in complex ways, leading to symptoms of addiction. The brain regions that are changed by drugs include the brain reward system as well as brain regions 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, also 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 the presence of drugs. However, addiction requires that these occur while a motivational form of dependence — the feeling that a person can’t live without a drug — also is developing.

An important question for addiction research is to understand how these many factors interact to predispose individuals to addiction and, conversely, how to protect them. The knowledge and insight into abuse and addiction arising from this research will lead to new therapies.

Alcohol Although legal, alcohol is addictive. Alcohol abuse and alcohol addiction — sometimes referred to as alcoholism or alcohol dependence — together are one of the nation’s major health problems.

Nearly 14 million people abuse alcohol or are alcoholic. Fetal alcohol syndrome, affecting about 0.5 to 3 of every 1,000 babies born in the United States, is the leading preventable cause of mental retardation. Cirrhosis, the main chronic health problem associated with alcohol addiction, and other chronic liver diseases are responsible for more than 25,000 deaths each year. The annual cost of alcohol abuse and addiction is estimated at $185 billion.

Genetic and environmental factors contribute to alcoholism, but no single factor or combination of factors enables doctors to predict who will become an alcoholic.

Alcohol activates the endogenous opioid system so that susceptible individuals may feel an opioidlike euphoria from their own endorphins when they drink. Based on animal research showing that opiate receptors were involved in the dopamine-reward activation of alcohol, naltrexone, a medication developed for heroin addiction, was used to treat alcoholics. Clinical trials began in 1983, and in 1995, naltrexone was approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcoholism.
Ethanol, the active ingredient in alcoholic beverages, reduces tension, and inhibitions. In low doses, it may act as a stimulant, whereas at higher doses, it acts as a depressant. In both cases, it significantly alters mood and behavior. It 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) receptor that recognize the neurotransmitter glutamate. This interaction can cloud thinking and eventually lead to coma.

**Club drugs**

Ecstasy, herbal ecstasy, Rohypnol (“roofies”), GHB (gamma hydoxybutyrate), 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 psychotropic 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 to 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 ingested unknowingly. 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.

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.

**Marijuana**

This drug distorts perception and alters the sense of time, space, and self. In certain situations, marijuana can produce intense anxiety.

In radioactive tracing studies, scientists found that tetrahydrocannabinol (THC), the active ingredient in marijuana, binds to specific 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 may explain why heavy users or those intoxicated on marijuana have poor short-term memory and problems processing complex information. Scientists recently discovered that these receptors normally bind to natural internal chemicals termed endocannabinoids, one of which is called anandamide. A large effort is now addressing the development of medications that target the endogenous cannabinoid system, with the hope that these will prove beneficial in treating a number of different brain disorders, including addiction, anxiety, and depression.

**Nicotine**

In 2003, more than 70 million people smoked, at least occasionally, making nicotine one of the most widely abused substances. Tobacco kills more than 430,000 U.S. citizens each year — more than alcohol, cocaine, heroin, homicide, suicide, car accidents, fire, and AIDS combined. Tobacco use is the leading preventable cause of death in the United States. Smoking is responsible for approximately 7 percent of total U.S. health-care costs, an estimated $80 billion each year. The direct and indirect costs of smoking are estimated at more than $138 billion per year.

Nicotine, the addictive substance in tobacco, acts through the well-known cholinergic 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. Nicotine also suppresses insulin output from the pancreas, which means that smokers are always slightly hyperglycemic. 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 transfer- mal 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 produce less severe physiological alterations than tobacco-based systems.

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, which directly interacts with the cholinergic nicotinic receptor in a key component 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.

**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 a brief 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. In large doses, heroin can make breathing shallow or stop altogether — the cause of death 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; in other words, they can curtail 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 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 over 500,000 patients in the United States.

**Psychostimulants**

This class of drugs includes cocaine and amphetamines. In 2003, there were an estimated 2.3 million chronic cocaine users and 5.9 million occasional cocaine users in the United States. 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 smokable form of methamphetamine, “crystal meth,” also has become popular. The key biochemical factor that underlies 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, and repeated use of these drugs progressively increases their ability to activate brain dopamine systems. This thought is resulted 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 and includes symptoms of emotional and physical exhaustion and depression. These symptoms result from an actual 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.

**Alzheimer’s disease**

One of the most frightening and devastating of all neurological disorders is the dementia that occurs in the elderly. The most common cause of this illness is Alzheimer’s disease (AD). Rare before age 60 but increasingly prevalent in each decade thereafter, AD affects more than 40 percent of those age 85 and over and nearly
HOW CRACK COCAINE AFFECTS THE BRAIN. Crack cocaine takes the same route as nicotine by entering the bloodstream through the lungs. Within seconds, it is carried by the blood to the brain. The basis for increased pleasure occurs at the gap where the impulses that represent neural messages are passed from one neuron to another. This gap is called a 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 neuron. Then, to and from 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 synapses. Pleasure circuits are stimulated again and again, producing euphoria.

20 percent of those ages 75 to 84. As many as 5 million Americans have AD. The disease is predicted to affect approximately 14 million individuals in the United States by the year 2040.

The earliest symptoms of AD include forgetfulness; disorientation to time or place; and difficulty with concentration, calculations, 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 bed-bound. Patients usually die from pneumonia or some other complication of immobility. AD, which in 2005 was reported to have killed 22,000 Americans, is the seventh leading cause of death in the United States.

In the earliest stages, the clinical diagnosis of possible or probable AD 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 AD 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 AD are not yet fully understood, but great progress has been made through genetics, biochemistry, cell biology, and experimental treatments. Reductions occur in levels of markers for many neurotransmitters, including acetylcholine, somatostatin, monoamines, and glutamate, that allow cells to communicate with one another. 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 AD brain tissue shows abnormal accumulations of a small fibrillar protein, termed beta amyloid, in the spaces around synapses (senile plaques) and abnormal accumulations of a modified form of the protein tau in the cell bodies of neurons (neurofibrillary tangles). In all forms of AD, plaques and tangles mostly develop in brain regions important for memory and intellectual functions. New brain imaging strategies show amyloid plaques and tau tangles labeled by a mildly radioactive chemical marker in living people.

Early-onset AD is a rare, dominantly inherited form of the disease. Recently, scientists have identified AD-associated mutations. The gene encoding the amyloid precursor protein (APP) is on chromosome 21. In other families with early-onset AD, 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 in late life, exists in three forms. The variant known as APOE epsilon 4 is clearly associated with enhanced risk.

Currently approved treatments do not modify the course of the disease and offer only temporary mitigation of some symptoms of AD, such as agitation, anxiety, unpredictable behavior, sleep disturbances, and depression. Five drugs have been approved by the FDA to treat AD. 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 improve memory deficits temporarily 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 AD-causing genes in mice. These mice, carrying mutant genes linked to inherited AD, 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 AD 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 but not in humans with the disease.

Researchers have begun to modulate the actions of genes that play critical roles in the production of amyloid in animal models. These genes encode the amyloid-producing enzymes beta and gamma secretases, which cleave amyloid peptide from the precursor. The amyloid peptide is then released from the neuron into the extracellular space, where it can accumulate and form AD plaques. Amyloid-degrading enzymes, known as alpha secretases, break up the amyloid peptide, preventing amyloid accumulation. Anti-amyloid therapies for AD 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 AD. Cognitive activity, physical activity, and heart-healthy diets lower the risk for AD, 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.

Amyotrophic lateral sclerosis

This progressive disorder strikes more than 5,000 Americans annually, with an average survival time of just three to five years from symptom onset. It is the most common disorder within a group of diseases affecting motor neurons and costs Americans some $300 million annually.

Commonly known as Lou Gehrig’s disease, amyotrophic lateral sclerosis (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 disease.

The first signs of progressive paralysis are usually seen in the hands and feet. They include weakness in the legs, difficulty walking, and clumsiness of the hands when washing and dressing. 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 muscle biopsies, blood studies, electrical tests of muscle activity, computed tomography (CT) and magnetic resonance imaging (MRI) scans, and X-rays
of the spinal cord help identify the disease and rule out other disorders. Still, diagnosis is often difficult because the causes of ALS remain unknown. Potential causes or contributors to the disease include glutamate toxicity, oxidative stress, environmental factors, and an autoimmune response in which the body’s defenses turn against body tissue.

In more than 90 percent of cases, ALS is sporadic, arising in individuals with no known family history of the disorder. 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 mutations in the gene that codes for superoxide dismutase. Scientists believe that whatever they learn from studying this gene and others will have relevance for understanding the more common sporadic form of motor neuron disease.

Once ALS is diagnosed, physical therapy and rehabilitation methods can help strengthen unused muscles. Various drugs can ease specific problems, such as twitching and muscle weakness, but there is no cure. An anti-glutamate drug moderately slows the disease. 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 hope for patients.

Anxiety disorders

The most widespread mental illnesses, anxiety disorders annually affect an estimated 12.6 percent of the adult population, or 24.8 million Americans. They include obsessive-compulsive disorder (OCD); panic disorder; phobias, such as fear of heights, agoraphobia (fear of open spaces), and social anxiety disorder; generalized anxiety disorder; and post-traumatic stress disorder (PTSD). Some can keep people completely housebound. Anxiety disorders often occur together with depression, and individuals doubly afflicted are at a high risk of suicide.

In OCD, people 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 5 to 6 million Americans annually. 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 OCD patients.

Scientists have recently discovered that certain breeds of dogs that develop acalcul dyskinesia, severely soar paws from compulsive licking, respond to the serotonergic antidepressant clomipramine, which was the first effective treatment developed for OCD in people. This and other serotonergic antidepressants and the selective serotonin reuptake inhibitors (SSRIs), such as serotonin and paroxetine, are effective in treating OCD. A specialized type of behavioral intervention, exposure and response prevention, also is effective in many patients.

Panic disorder, with a lifetime prevalence rate of 1.7 to 3.5 percent in the United States, usually starts “out of the blue.” 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 and avoid public settings where attacks might occur. If these patients 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, bugs, blood, 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.

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. Treated PTSD, the lifetime prevalence rate in the United States for this disorder is 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 the hypothalamic-pituitary-adrenal axis, disordered sleep, and major depressive disorder. Military personnel are at elevated risk for exposure to trauma and not surprisingly have higher prevalence rates when compared to the general population.

Scientists have learned that very high levels of norepinephrine are released in the brain during stress and that patients with PTSD have heightened levels of this chemical long after the traumatic event has passed. High levels of norepinephrine strengthen the primitive emotional reactions of the amygdala, the fear center of the brain, while weakening the rational functions of the prefrontal cortex, which quiet the amygdala. Very high levels of norepinephrine release can strengthen the consolidation of emotional memories and strengthen fear responses through the stimulation of alpha-1 and beta receptors in the amygdala. In contrast, stimulation of alpha-1 receptors in the prefrontal cortex takes the higher brain region “offline.” The prefrontal cortex normally allows us to suppress troubling memories and thoughts, and inhibits the amygdala to let us know that we are safe (the extinction of the fear response). Imaging studies show that patients with PTSD have weaker prefrontal function and stronger amygdala activation, consistent with their symptoms.

New successful medications for PTSD have arisen from this basic research. 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; those treated with prazosin include people with 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 close in time after the trauma, before PTSD has been established, which brings up complex ethical issues.

The discovery of brain receptors for the benzodiazepine anxiolytic drug has sparked research to identify the brain’s own anti-anxiety chemical messengers. The benzodiazepine receptors are a component of the GABA receptor and enhance the 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. This finding may lead to ways to regulate the brain system and correct its possible defects in anxiety disorders.

PTSD also is treated with antidepressant and antipsychotic anti- mediciations and with psychotherapies such as cognitive behavioral therapy or eye movement desensitization and reprocessing therapy.

Attention deficit hyperactivity disorder (ADHD)

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 2 million children in the United States, or 3 to 5 percent of children. Studies show that 30 percent to 70 percent of these children will continue to experience ADHD symptoms as adults.

By definition, symptoms of ADHD appear before age 7, last for six months or longer, and impair normal functioning in at least two types of settings — at school, among friends, at home, or at work, in the case of adults. Currently, no objective diagnostic test for ADHD exists. Diagnosis requires a comprehensive evaluation, including a clinical interview, parent and teacher ratings, and, sometimes, learning disorder or psychological testing. Multiple evaluation techniques are required because healthy children occasionally show similar behavior, and other conditions, disorders, or environmental triggers — such as stress — may be associated with the same behaviors.

Twins and family studies show that ADHD has a strong genetic influence, and genes encoding components of dopamine and norepinephrine transmission have been implicated. Studies increasingly are finding correlations between ADHD and differences in brain volume or function. Smaller volume and reduced activity are often observed in prefrontal cortical-striatal-cerebellar circuits, particularly in the right hemisphere. Recent studies show a delay in cortical development in some children with ADHD, speculated to represent the subgroup who “grow out” of the disorder.

Recent imaging studies are consistent with reduced catecholamine transmission in at least some patients with this disorder.

As 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 medications such as stimulants (e.g., methylphenidate) and newer, nonstimulant drugs. These agents all act by enhancing catecholamine transmission in the prefrontal cortex. Despite the widespread use of stimulants, concerns about their risks linger. Thus, parents and clinicians have to balance the benefits of a child with better attention and behavioral regulation on one hand, and the uncertainty about the risks of exposing children to psychotropic drugs on the other.

Autism

An autism spectrum disorder (ASD) is diagnosed in 1 of every 150 babies born in the United States (approximately 1.7 million Americans), an incidence greater than in the 1970s owing mainly to changes in diagnostic criteria, grouping of multiple disorders into one spectrum, and enhanced clinician referral based on greater awareness. ASD is characterized by communication difficulties; absent, delayed, or abnormal language; impaired social skills; and narrow, obsessive interests or repetitive behaviors. Common associated symptoms include mental retardation, seizures, and behavioral abnormalities.
Currently, ASD is diagnosed in 3- to 5-year-olds based on behavioral symptoms. New research indicates that very sensitive measures of social engagement and interaction can detect differences in the first year of life, a time when many affected children exhibit accelerated growth of the brain. This abnormal growth is a potential marker for early evaluation that may also indicate that development has gone awry.

Studies of brain neurophysiology, tissue, and imaging indicate that ASD is a disorder that disrupts basic developmental processes that occur both before and after birth, potentially including neural cell proliferation, migration, survival, axon and dendrite extension, and synapse formation. Specific brain regions involved in language, cognition, and social communication, or the connections among them, may be formed abnormally. Research also indicates that genetic factors are major contributors to ASD (10 to 20 percent of cases have identified genetic causes), with potential involvement of environmental factors. Although no cure exists, many affected children respond well to highly structured environments and specialized education and language programs, with earlier interventions leading to better outcomes. Associated symptoms respond to medications.

Knowledge of specific functional deficits in social and cognitive circuits is leading to distinct clinical training to improve brain activity and behavioral outcomes, whereas genetic findings may allow new targeted therapies at the molecular level. One day, genetic tests may complement behavioral indicators to allow earlier diagnosis and intervention as well as the means to overcome and possibly prevent ASD symptoms.

Bipolar disorder

Patients with bipolar disorder, previously known as manic-depressive illness, usually experience episodes of deep depression and manic highs, with a return to relatively normal functioning in between. They also have an increased risk of suicide. Bipolar disorder annually affects 1.2 percent of Americans age 18 or older, or 2.2 million individuals. Approximately equal numbers of men and women suffer from this disorder.

Bipolar disorder tends to be chronic, and episodes can become more frequent without treatment. As bipolar disorder runs in families, efforts are underway to identify the responsible gene or genes. Bipolar patients can benefit from a broad array of treatments. One of these is lithium. During the 1940s, researchers showed that lithium injections into guinea pigs made them placid, which implied mood-stabilizing effects. When given to manic patients, lithium calmed them and enabled them to return to work and live relatively normal lives. Regarded as both safe and effective, lithium is often used to prevent recurrent episodes.

Other useful medications include certain anticonvulsants, such as valproate or carbamazepine, which can have mood-stabilizing effects and may be especially useful for difficult-to-treat bipolar episodes. Newer anticonvulsant medications are being studied to determine how well they work in stabilizing mood cycles.

Brain tumors

Although brain tumors are not always malignant — a condition that spreads and becomes potentially lethal — these growths always are serious because they can interfere with normal brain activity.

Primary brain tumors arise within the brain, whereas metastatic (also called secondary) brain tumors spread from other parts of the body through the bloodstream. The incidence of primary brain tumors is about 15 per 100,000. About 44,000 new cases occur in the United States annually.

Symptoms vary according to location and size, but seizures and headache are among the most common. To expand, gliomas, typically malignant brain tumors, release the neurotransmitter glutamate at toxic concentrations. This kills off neurons in their vicinity, making room for the tumor’s expansion. The released glutamate explains seizures originating 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.

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 is not very effective for gliomas. Steroid drugs relieve brain swelling, and anti-epileptic drugs control seizures.

New therapies for brain tumors are developed in organized studies called clinical trials. Many of these trials focus on targeted therapy — treatment aimed at 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, in which the tumor’s blood supply is restricted; immunotherapy, which uses the body’s own immune system against the tumor; gene therapy, in which biogenetically engineered genes are delivered 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 that interferes with tumor spread has shown promise in clinical studies where it extended life expectancy significantly.

Researchers are exploring the role of stem cells in the origin of brain tumors. Epidemiologists, or scientists studying disease in human populations, also are looking into tumor genetics and patients’ lifestyle, environment, occupation, and medical history for clues as to the causes of these tumors. International efforts are underway to increase awareness of brain tumors, encourage research collaborations, and explore new and innovative therapies.

Down syndrome

Down syndrome, the most frequently occurring chromosomal condition, appears in 1 of every 732 babies. It typically occurs when an extra copy of chromosome 21 — or part of its long arm — is present in the egg or, less commonly, in the sperm, at the time of conception. It is not known why this error occurs, and the error 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 35, the risk is about 1 in 365 births; at age 40, it is 1 in 110. 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 Screens, 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. Nearly all people with Down syndrome show some neuro-pathological changes like those seen in Alzheimer’s disease by age 40, and most show cognitive decline by age 60.

Babies with Down syndrome develop much as typical children do but at a somewhat slower rate. They learn to sit, walk, talk, and toilet train, just like their peers. 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 or means of preventing Down syndrome, scientists are moving closer to understanding the role that the genes on chromosome 21 play in a person’s development.

Once this mystery is understood, they hope to decode the biochemical processes that occur in Down syndrome and learn to treat or cure this disorder.

Dyslexia

An estimated 15 to 20 percent of the population, as many as 60 million Americans, has some form of learning disability involving difficulties in the acquisition and use of listening, speaking, reading, writing, reasoning, or mathematical abilities. These challenges often occur in people with normal or even high intelligence.

Dyslexia, or 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. Dyslexia is characterized by an unexpected difficulty in reading in children and adults who otherwise possess the intelligence, motivation, and schooling 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 — and more specifically, in a component of the language system called phonology. This results in difficulty transforming the letters on the page to the sounds of language.

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, for instance 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 using functional brain imaging indicates that dyslexic readers demonstrate a functional disruption in an extensive system in the posterior portion of the brain. The disruption occurs within the neural systems linking visual representations of letters to the phonologic structures they represent, and the resulting brain images are referred to as the neural signature of dyslexia.

It is clear that dyslexia runs in families, and research has advanced understanding of its genetic basis. Following the gradual identification over the past 22 years of sites on the human genome that are associated with an increased risk for developing dyslexia, in the past four years, six candidate dyslexia susceptibility genes have been reported, and multiple studies have confirmed some of these candidates. These risk alleles, the term given to variant genes that increase the risk of developing a condition or illness, have been shown to play important roles in the development of the brain during fetal life, and some of them may eventually be confirmed to play a role in 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 a role in dyslexia.

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A microscope suggests that abnormalities are present principally in such as CT and MRI, show that the brains in these patients have leg weakness and a loss of balance. Imaging techniques, slowing of their mental processes. At the same time, patients may mon early in HIV infection. Later, however, patients develop neuropa thy, nerve death in extremities that causes severe pain, is also a major neurological problem commonly seen in HIV patients. It is believed that the virus triggers a distal sensory neuropathy through neurotoxic mechanisms. This has often been unmask ed or exacerbated by certain antiretroviral drugs that have mitochondrial toxicity and tend to make the neuropathies more frequent and serious. More than half of advanced patients have neuropathy, making it a major area for preventive and symptomatic therapeutic trails.

Despite remarkable advances toward new therapies, some patients develop these neurological problems and fail to respond to treatment, thus requiring additional approaches to prevention and treatment of the symptoms. In addition, because of immunodefi ciency in HIV patients, otherwise rare opportunistic infections and malignancies are relatively common.

Neurological trauma

Some 1.4 million people suffer traumatic head injuries each year in the United States, of whom roughly 50,000 die. Those who survive face a lifetime of disability, and economic costs approach $62 billion annually.

No magic bullet has yet been found, but doctors have discovered several methods to stave off severe neurological damage caused by head and spinal cord injuries and to improve neurological function following trauma. These treatments include better imaging techniques, methods to understand and improve the brain’s ability to regenerate and repair itself, and improved rehabilitation techniques.

Greater access to and use of CT and MRI offer physicians the opportunity to diagnose the extent of trauma and to avoid secondary injury related to edema, or swelling, and a reduction in blood flow to the brain (ischemia). 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 increases in intracranial pressure include the removal of cerebrospinal fluid, moderate hyperventilation to decrease blood volume, and the administration of drugs to reduce cellular metabolism or to remove waste from the injured tissue. 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 52 percent, and 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 in intracranial pressure, this results in an increase in blood flow, allowing more blood to reach vital areas.

In addition to helping the physician avoid cerebral edema and reductions in cerebral blood flow following traumatic brain injury, imaging can reveal mass lesions produced by the initial injury. These mass lesions can consist of bleeding on the surface or within the brain as the formation of contusions (bruises). Once blood leaks from vessels and comes into direct contact with brain tissue, it can add focal pressure, thereby reducing cerebral blood flow, or can by itself be toxic to brain cells. As a consequence, it may be removed surgically. 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 craniotomy.

An estimated 250,000 individuals are living with spinal cord injury in the United States. Some 11,000 new injuries are reported annually and are caused mostly by motor vehicle accidents, sports in jury, violence, and falls. Economic costs approach $10 billion a year.

Researchers have found that people who suffer spinal cord injuries may become less severely impaired if they receive high intravenous doses of a commonly used steroid drug, methylprednisolone, within eight hours of the injury. Building on these clues and insight 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.

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 discovered that new nerve cells can be born in the adult brain, but these new cells do not seem capable of helping 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 to overcome or 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 promote nerve regeneration after brain and spinal cord injury. Although these new therapies have not yet reached the clinic, several approaches are on the path to clinical trials.

Pain

If there is universal experience, pain is it. Each year, more than 97 million Americans suffer chronic, debilitating headaches or a bout with a bad back or the pain of arthritis—again, 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 mes sages have paved the way for new treatments for both chronic and acute pain.

Local anesthetics, 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 inter rupt 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 was used by dentists. Lidocaine is more popular today.

Analgesia refers to the loss of pain sensation. The four main types of analgesics are nonsteroidal anti-inflammatory drugs, or NSAIDs, such as ibuprofen and aspirin; opioids, such as codeine, with aspirin or an NSAID. Opioids are the most potent anti-inflammatories and pain-producing chemical prostaglandins. Opiate analgesics have a wide range of effects on the body, including some neuropathic pain conditions where light touch of the skin can be painful. Some neuropathic pain conditions where light touch of the skin can be painful.
to block pain impulses in the brain itself. Local anesthetics intercept pain signals traveling up the nerve. Opiate drugs, Aspirin, which acts primarily in the periphery, prevents the production of prostaglandins. Acetaminophen is believed (e.g., constipation results from morphine’s action on opioid receptors) that are predominantly, if not exclusively, expressed by nociceptor targets are specialized receptor channels (one of which is activated by capsaicin, the pungent ingredient in hot peppers, and another by mustard oil) and 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 of drugs that target these molecules in humans may have great value for the treatment of acute and persistent pain.

However, it should be emphasized that pain experience is the product of brain function. The pain is in the brain, not in the nociceptors that respond to the injury. In addition to the sensory-discriminative aspects, pain involves emotional factors and the meaning of previous painful experiences, which need to be addressed concurrently in order to treat pain. The fact that placebo and hypnosis can significantly reduce pain clearly illustrates the importance of these psychological factors. New targets for the treatment of pain also include approaches that identify molecules in the brain associated with the elaboration of persistent pain.

Parkinson’s disease

This neurologic disorder affects 1 million individuals in the United States, most of whom are older than 50. Parkinson’s disease is characterized by symptoms of slowness of movement, muscular rigidity, tremor, and postural instability.

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 the successful treatment of this disorder by administration of the drug levodopa, which is converted to dopamine in the brain. The successful treatment of Parkinson’s by replacement therapy is one of the greatest success stories in neurology.

Levodopa is now combined with another drug, carbidopa, that reduces the peripheral breakdown of levodopa, thus allowing greater levels to reach the brain and reducing side effects. Also playing an important role are newer drugs, such as inhibitors of dopamine breakdown and dopamine agents.

Genetic studies have demonstrated several heritable gene abnormalities in certain families, but most cases of Parkinson’s occur sporadically. It is believed, however, that hereditary factors may render some individuals more vulnerable to environmental factors, such as pesticides. The discovery in the late 1970s that a chemical substance, MPTP, can cause parkinsonism in drug addicts stimulated intensive research on the causes of the disorder. MPTP was accidentally synthesized by illicit drug designers seeking to produce a heroinlike compound. MPTP was found to be converted in the brain to a substance that destroys dopamine neurons. Parkinson’s continues to be studied intensively in both rodent and primate MPTP models.

In the past several decades, scientists have shown in primate models of Parkinson’s that specific regions in the basal ganglia, a group of cellular structures deep in the brain, are abnormally overactive. Most important, they found that surgical destruction or deep-brain stimulation. 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. The past decade has also seen further attempts to treat such patients with surgical implantation of cells, such as fetal cells, capable of producing dopamine. Replacement therapy with stem cells also is being explored. More recently, gene transfer of trophic factors has been studied in animal models and is being tested in clinical trials. Lastly, four clinical trials are currently underway testing the hypothesis that gene therapy can provide symptomatic (in some cases) or neuroprotective (in others) benefit to patients with Parkinson’s.

Schizophrenia

Marked by disturbances in thinking, emotional reactions, and social behavior, schizophrenia usually results in chronic illness and personality change. Delusions, hallucinations, and thought disorder are common.

Affecting about 1 percent of the population, or 2 million Americans each year, schizophrenia is disabling and costly.

On a given day, these patients occupy up to 100,000 hospital beds. Annual costs total about $32.5 billion.

Schizophrenia is thought to reflect changes in the brain, possibly caused by disruption of neurodevelopment through 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 pathogenesis of the disorder. Recently, 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 exacerbated by life stresses. About 15 percent of patients 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. The negative symptoms may be the most debilitating in terms of leading a productive life and generally are resistant to drug treatment.
Seizures and epilepsy

Seizures are due to sudden, disorderly discharges of interconnected neurons in the brain that temporarily alter one or more brain functions. Epilepsy is a chronic neurological disorder characterized by the occurrence of unprovoked seizures. In developed countries, epilepsy affects approximately 50 of every 100,000 people. It affects three to four times that number in developing countries.

Many different types of epilepsy have been recognized. Epilepsy can start at any age and can be idiopathic (having 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 are of two types, generalized and 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 arise when there is simultaneous excessive electrical activity over a wide area of the brain, often involving the thalamus and cerebral cortex. In partial seizures, seizures typically occur with maintained consciousness or with altered awareness and behavioral changes. Partial seizures can produce localized visual, auditory, and skin sensory disturbances; repetitive uncontrolled movements; or confused, automatic behaviors.

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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 90 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 antiepileptic drugs.

Surgery is an excellent option for patients with specific types of partial seizures who do not respond to antiepileptic drugs. Surgery requires the precise location and removal of the brain area from which the partial seizures originate. 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 implantable pacemakerlike 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. This deprives the brain 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 was no treatment. 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, the clot-dissolving bioengineered drug, tissue plasminogen activator (tPA), is now a standard treatment in many hospitals. This approach rapidly opens blocked vessels to restore circulation before oxygen loss causes permanent damage. Given within three hours of a stroke, it can often 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 from devising ways to protect these neurons.

Stroke affects roughly 700,000 Americans a year — 150,000 of whom die; total annual costs are estimated at $51.2 billion. Stroke often occurs in individuals over 65 years of age, yet a third are younger.

Stroke tends to occur more in males and African Americans and 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 can help prevent stroke. Other specific treatments involving surgery or arterial stents can clear clots in the arteries of the neck region; these and treatments targeting heart disease can help prevent a cutoff of blood supply. Antidepressant drugs can reduce the likelihood of clot 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 can aid 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 aids recovery even if administered several days after the injury. Administration of growth factors may further enhance the benefits of stem cell transplantation.

Tourette syndrome

One of the most common and least understood neurobiological disorders, Tourette syndrome (TS) is an inherited disorder that affects about 1 in 200 Americans. Males are affected three to four times as often as females. Symptoms usually appear between the ages of 4 and 8, 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 and 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 TS also have associated conditions such as problems with learning, difficulties with attention, and 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.

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

The majority of people with TS are not significantly disabled by symptoms, and therefore 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, that are prescribed for attention deficit hyperactivity disorder (ADHD) have been reported to improve attention and decrease tics in TS. 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 patient and must be gauged carefully by a doctor. The medication is administered in small doses with gradual increases to the point where there is a 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, all of which can be reduced with specific medications. Some side effects such as depression and cognitive impairment can be alleviated with dosage reduction or a change of medication.

Other types of therapy also may be helpful. Psychotherapy and counseling can assist people with TS and help their families cope, and some behavior therapies can be very effective in reducing the severity of both tics and compulsions.

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Magnetic resonance spectroscopy (MRS) is a technique related to MRI. MRS 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 on 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.

Functional magnetic resonance imaging (fMRI) Among 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, which is a correlate for 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, and 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 respond.

One of the most exciting developments in imaging is the combined use of information from fMRI and MEG. Together, this information leads to a much more precise understanding of how the brain works in health and disease.
New hereditary linkage studies have made it possible to find the chromosomal location of genes responsible for neurologic and psychiatric diseases and to identify structural changes in these genes that are responsible for causing disease.

Evaluation of the malignancy of certain tumors and people’s susceptibility to them.

So far, scientists have found the chromosomal location of defective genes for more than 100 neurologic disorders and have identified the defect in up to 50. Prenatal or carrier tests exist for many of the most prevalent of these diseases.

For example, scientists have tracked down the gene that goes awry in Huntington’s patients. The defect is an expansion in the gene coding for the beta amyloid precursor protein that is abnormally cut to form the smaller peptide, beta amyloid. It is this peptide that accumulates in the senile plaques that clog the brains of patients with Alzheimer’s disease. This discovery shed light on why individuals with Down syndrome with three copies of chromosome 21 (trisomy 21) invariably accumulate amyloid deposits; they make too much amyloid because they have an extra copy of this gene. Mutations in this gene have been shown to underlie Alzheimer’s in another subset of these patients.

Gene mapping has enabled doctors to diagnose fragile X mental retardation, the most common cause of inherited mental retardation in males. Some scientists have now identified this gene, FMR1, which is found on the X chromosome and is important for neuronal communication. Other groups of scientists are investigating whether genetic components to schizophrenia, bipolar disorder, and alcoholism exist, but their findings are not yet conclusive.

Overall, the characterization of the structure and function of individual genes causing diseases of the brain and nervous system are in the early stages. Factors that determine variations in the genetic expression of a single-gene abnormality — such as what contributes to the early or late start or severity of a disorder or prevents its occurrence in a mutant gene carrier — are still largely unknown.

Scientists are also studying the genes in mitochondria, structures found outside the cell nucleus that have their own DNA and are responsible for the production of energy used by the cell. Recently, mutations in mitochondrial genes were found to cause severe rare neurologic disorders. Some scientists speculate that an inheritable variation in mitochondrial DNA may play a role in diseases such as Alzheimer’s, Parkinson’s, and some childhood diseases of the nervous system.

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 new fields 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. A scientist then 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, 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 trophic factors, antibodies engineered to modify the interactions and toxicity of misfolded proteins, 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 growth factors or trophic factors, which control the development and survival of specific groups of neurons. Neuroscientists have discovered that certain specific molecular signals and mitogenic factors are present in the brain and in the spinal cord that can stimulate the regeneration of damaged neurons. This has led to the development of compounds called “neurotrophics,” which can promote the growth and survival of damaged neurons.

Engineered antibodies

The immune system has evolved to very specifically identify and modify factors both inside and outside of cells. It is sometimes possible to trick the body into attacking proteins that cause neurologic diseases by “vaccinating” patients against these proteins.
This approach has shown some promise in 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.

Several neurodegenerative diseases are caused by the accumulation of abnormal proteins. If the cells made much less of such proteins to begin with, then presumably the disease 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 HD 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 embryonic 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. A more limited type of stem cell also has been discovered in the adult nervous system in various kinds of tissue, raising the possibility that these adult stem cells might be pharmacologically directed to replace damaged neurons.

In other work, researchers are studying a variety of viruses that may ultimately be used as “Trojan horses,” carrying therapeutic genes to the brain to correct nervous system diseases. Adeno-associated virus (AAV) and human or equine lentivirus seem to be the safest and most efficient at this time. AAV and equine lentivirus are being used in clinical trials in patients with PD. Herpes simplex virus and adeno-associated virus vectors also have been evaluated in early-stage human trials for treating brain tumors.
NEUROETHICS

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. This is no different for neuroscientists. With the tremendous advances in the field, scientists and nonscientists alike have sensed a critical turning point. Advancing knowledge about how the brain enables 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 areas responsible for phenomena such as deception. The post-9/11 era has created much interest in lie detection for security purposes in screening immigrants. How should privacy be balanced with national security? Is the technology accurate enough to provide useful data upon which to base decisions? Pursuing these lines of scientific inquiry in a responsible way requires neuroscientists to examine how they affect the world beyond the laboratory or clinic.

Self-examination 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 such as brain scanning, brain stimulation, and pharmaceuticals to 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. What’s more, brain science is developing interventions that can change the way our brains function. Neuroethics links the descriptive science — what we do — with the questions of what we should be.

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 policy-makers 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 where gaps exist between diagnosis and treatment, where treatments may offer tradeoffs in personality or cognitive changes, and where drugs or devices that can help unwlial patients also can boost performance of normal people. When diagnostic tests exist for brain-based diseases that have no cure, such as Alzheimer’s, how should this capability 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?

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 to pictures of minority groups within a society. What are we to make of such information? Will it help us understand prejudice, or could it be used to influence decisions about individuals? Is critical that scientists explain the limitations of current technologies and help formulate policies to minimize the chances of misuse.

Prediction

Neuroimaging and genetic screening may enable us to predict behavior, personality, and disease with greater accuracy than ever before. Neuroimagining technology is also being researched and marketed for lie detection, with 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. Our approximately 20,000 genes are very distant from our behavior, however, and appear to act in extremely complex combinations in contributing to neural function. Neuroscience technologies that enable more accurate assessment also raise important concerns about privacy and fairness that go beyond those in bioethics. Will we be able to use imaging to measure intelligence? Empire? Risk for violence? What degree of privacy do we have to expect over our thoughts? If someone has not yet committed a crime but shows brain-based reactions to inappropriate stimuli, such as pictures of children, would we require further monitoring or even preventive detention? The neuroimaging detection of lying has the potential to support a major impact on society but will require careful controls and years of research. 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 that technologies evolve.

Informed consent in research

Special care must be taken when scientists seek consent to conduct research and throughout experiments, when individuals 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.
**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.

**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.

**APOPTOSIS** Programmed cell death induced by specialized biochemical pathways, often serving a specific purpose in the development of the 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.

**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.

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

**CENTRAL NERVOUS SYSTEM** A major cause of dementia in the elderly, often as a result of a stroke.

**CEREBRAL CORTEX** The outermost layer of the cerebral hemispheres of the brain. It is largely responsible for all forms of conscious experience, including perception, emotion, thought, and planning.

**CEREBRAL HEMISPHERES** The two specialized halves of the brain. For example, in right-handed people, the left hemisphere is specialized for speech, writing, language, and calculation; the right hemisphere is specialized for spatial abilities, visual face recognition, and some aspects of music perception and production.

**CEREBROSPINAL FLUID** A liquid found within the ventricles of the brain and the central canal of the spinal cord.

**CLASSICAL CONDITIONING** Learning in which a stimulus that naturally produces a specific response (unconditioned stimulus) is repeatedly paired with a neutral stimulus (conditioned stimulus). As a result, the conditioned stimulus can come to evoke a response similar to that of the unconditioned stimulus.

**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.

**CORTISOL** A hormone, released by the adrenal medulla and specialized sites in the brain, that acts with norepinephrine to affect the sympathetic division of the autonomic nervous system. Sometimes called adrenaline.

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

**CURTIS** A large structure located at the root of 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.

**DENDRITE** A tree-like extension of the neuron cell body. The dendrite is the primary site for receiving and integrating information from other neurons.

**DOPAMINE** A catecholamine neurotransmitter known to have varied functions depending on where it acts. Dopamine-containing neurons in the substantia nigra of the brainstem project to the caudate nucleus and are destroyed in Parkinson’s victims. Dopamine is thought to regulate key emotional responses and plays a role in schizophrenia and drug abuse.

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

**ENDOCRINE ORGAN** 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.

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

**EVOKED POTENTIAL** A measure of the brain’s electrical activity in response to sensory stimuli. This is obtained by placing electrodes on the surface of the scalp (or more rarely, inside the head), repeatedly administering a stimulus, and then using a computer to average the results.

**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.
HAIR CELLS

Most axons. It is the site where new material is added to the axon.

MEMORY

Of the most studied areas of the brain, it functions in learning, including regulation of heart rate, respiration, pain perception, and movement.

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).

MONOAMINO OXIDASE (MAO)

The brain and liver enzyme that normally breaks down the catecholamines norepinephrine, dopamine, and epinephrine, as well as other monoamines such as serotonin.

NEURON

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

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

Compact fatty material that surrounds and insulates the axons of some neurons.

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 developing animals.

NECROSIS

Cell death due to external factors, such as lack of oxygen or physical damage, that disrupt the normal biochemical processes in the cell.

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.

NEURON

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

NEUROPLASTICITY

The process of change that occurs in the brain and nervous system in response to injuries to the nervous system or alterations in patterns of their use and disease.

NEUROTRANSMITTER

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

NOCEPторS

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 in regulation of sleep, 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.

PERIPHERAL NERVOUS SYSTEM

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

PHOSPHORYLATION

Transfer of a phosphate molecule from adenosine triphosphate (ATP) to a protein (an ion channel, neurotransmitter receptor, or other regulatory protein), resulting in activation or inactivation of the protein. Phosphorylation is believed to be a necessary step in allowing some neurotransmitters to act and is often the result of second-messenger activity.

PHOTORECEPTOR

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

PITUTARY 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.

PONS

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

GAMMA-AMINO BUTYRIC ACID (GABA)

A neurotransmitter whose role is to inhibit the firing of nerve cells.

GONAD

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

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 vibration to an electrical signal; they in turn excite the 30,000 fibers of the auditory nerve that carry the signals to the brain.

IONS

Electrically charged atoms or molecules.

IONIC CONDUCTION

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

HYPERPLASIA

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.

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

RECEPTOR CELL A specialized sensory cell, designed to pick up and transmit sensory information.

RECEPTOR MOLECULE A specific protein on the surface of or inside a cell with a characteristic chemical and physical structure. Many neurotransmitters and hormones exert their effects by binding to receptors on cells.

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 night vision.

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

SECOND MESSAGERS Substances that trigger communications among different parts of a neuron. These chemicals play a role in the manufacture and release of neurotransmitters, intracellular movements, carbohydrate metabolism, and processes of growth and development. The messengers’ direct effects on the genetic material of cells may lead to long-term alterations of behavior, such as memory and drug addiction.

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 play a role in many roles, including but not limited to temperature regulation, carbohydrate metabolism, and processes of growth and development.

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

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.

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