

BRAIN DEVELOPMENT

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 embryo. 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 so they 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.

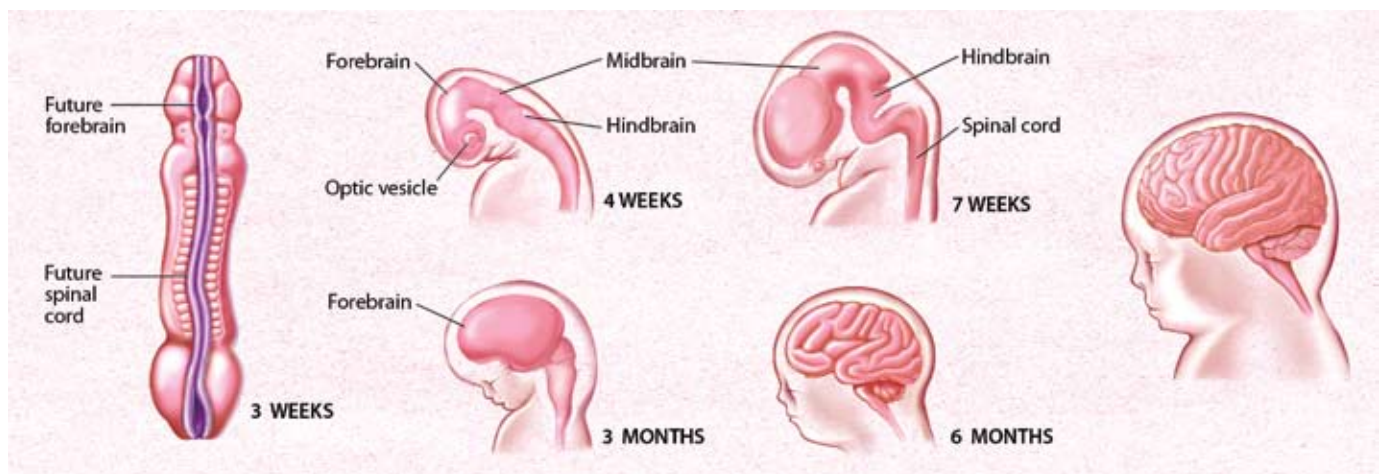
Advances in the study of brain development have become increasingly relevant for medical treatments. For example, several diseases that most scientists once thought were purely disorders of adult function are now being considered in developmental terms,

including schizophrenia. Other research suggests that genes that are important for brain development may also play a role in susceptibility to autism spectrum disorders. And by applying knowledge about how connections form during development, regeneration following injury to the brain now is viewed as distinctly possible.

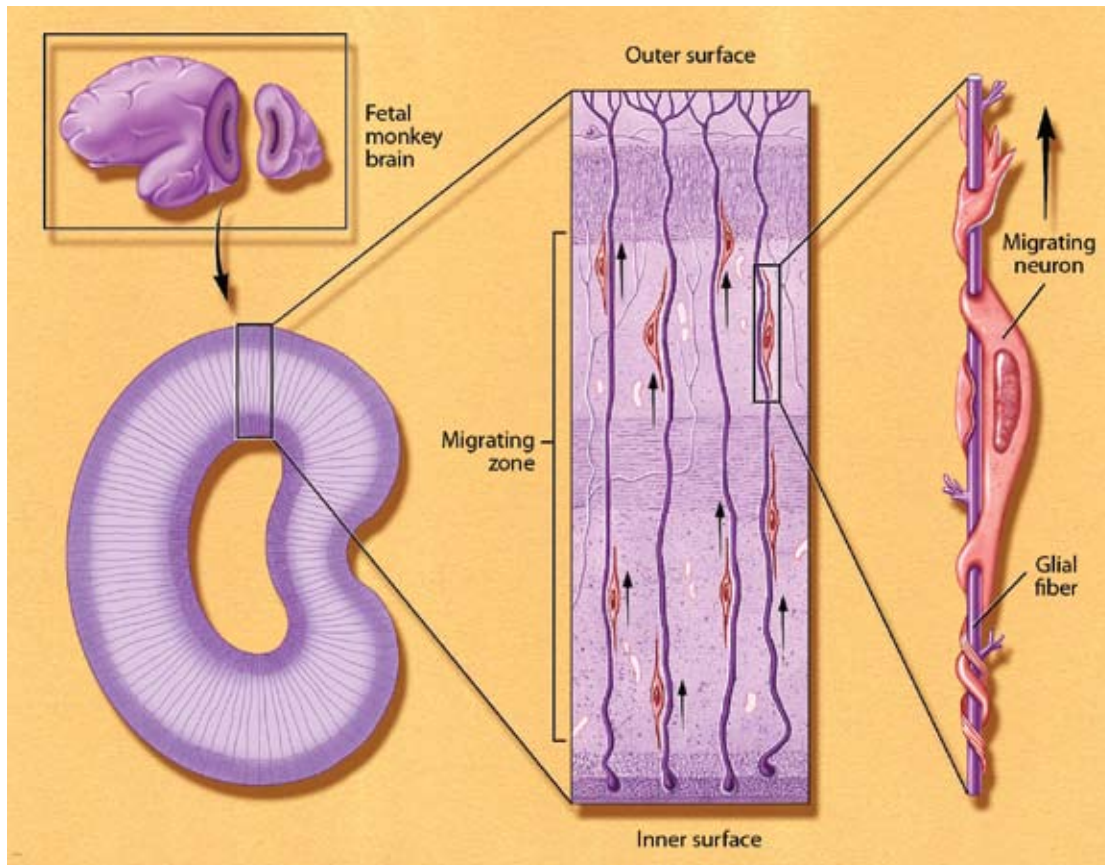
Knowing how the brain is put together is essential for understanding its ability to reorganize in response to external influences or injury. These studies also shed light on brain functions such as learning and memory. The brain evolves from the embryo to the adult stage, and during infancy and childhood it possesses unique attributes that contribute to differences in learning ability as well as vulnerability to specific brain disorders. Neuroscientists are beginning to discover some general principles that underlie developmental processes, many of which overlap in time.

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 fuse to form 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.



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.



NEURON MIGRATION

A cross-sectional view of the occipital lobe (which processes vision) 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. To move, it needs adhesion molecules, which recognize the pathway, and contractile proteins to propel it along.

The embryo has three layers that undergo many interactions in order to grow into organ, 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 with other cells, such as cardiac, or heart, tissue, they produce the neurotransmitter acetylcholine. Since all neurons have the genes required to produce these molecules, it is the turning on of a particular set of genes that begins the production of specific neurotransmitters. Many researchers believe that the signal to engage the gene and, therefore, the final determination of the chemical messengers that a neuron produces, is influenced by factors coming from the targets themselves.

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 meet thicker 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.

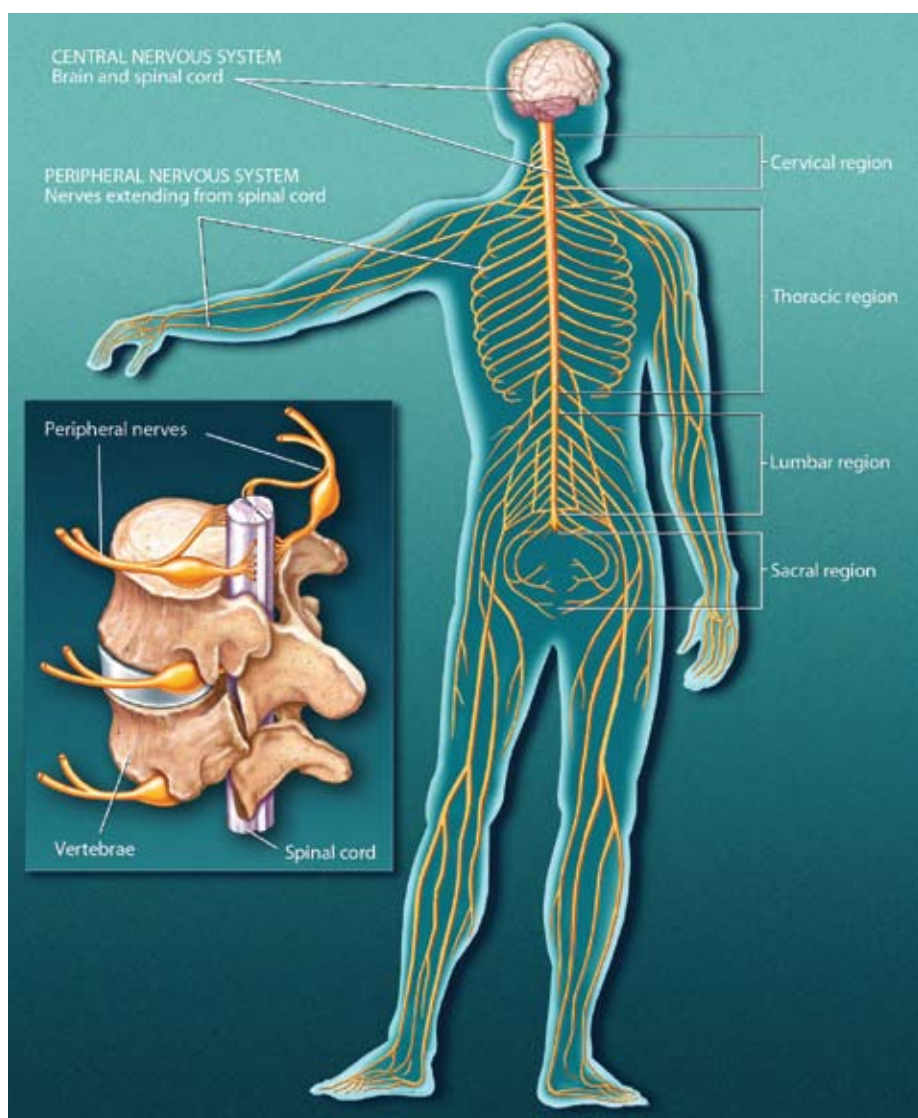
Axon growth is directed by growth cones. These enlargements of the axon's tip actively explore the environment as they seek out their precise destination. Researchers have discovered many special molecules that help guide growth cones. Some molecules lie on the cells that growth cones contact, whereas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

sources found near the growth cone. The growth cones, in turn, bear molecules that serve as receptors for the environmental cues. The binding of particular signals with receptors tells the growth cone whether to move forward, stop, recoil, or change direction. These signaling molecules include proteins with names such as netrin, semaphorin, and ephrin. In most cases, these are families of related molecules; for example, researchers have identified at least 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 protein family is smaller in flies or worms than in mice or people, but its functions are quite similar. It has therefore been possible to use the simpler 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.

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 sending 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,



SPINAL CORD AND NERVES. The mature central nervous system (CNS) consists of the brain and spinal cord. The brain sends nerve signals to specific parts of the body through peripheral nerves, known as the peripheral nervous system (PNS). Peripheral nerves in the cervical region serve the neck and arms; those in the thoracic region serve the trunk; those in the lumbar region serve the legs; and those in the sacral region serve the bowels and bladder. The PNS consists of the somatic nervous system that connects voluntary skeletal muscles with cells specialized to respond to sensations, such as touch and pain. The autonomic nervous system is made of neurons connecting the CNS with internal organs. It is divided into the sympathetic nervous system, which mobilizes energy and resources during times of stress and arousal, and the parasympathetic nervous system, which conserves energy and resources during relaxed states.

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.

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. Communica-

tion between neurons with chemical and electrical signals is necessary to weed out the connections. The connections that are active and generating electrical currents survive, whereas those with little or no activity are lost. Thus, the circuits of the adult brain are formed, at least in part, by sculpting away incorrect connections to leave only the correct ones.

Critical periods

Although most of the neuronal cell death occurs in the embryo, the paring 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

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affect one aspect of development, whereas the same injury at a different period may affect another aspect.

In one example, if a monkey is raised 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.

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. Research results indicate the need to understand processes related to normal function of the brain at each of its major stages and suggest that this information might lead to better age-specific therapies for brain disorders.