Learning Objectives

After reading this chapter, you will be able to:

- Describe the neuroanatomy and neurophysiology of the brain in relation to mental health and illness.
- Explain the basic processes of neurotransmission and the role of neurotransmitters in the major mental disorders.
- Explain the neurobiologic rationale for the pharmacologic treatment of the major mental disorders.

Key Terms

Allostatic load
Amine neurotransmitters
Amygdala
Apraxia
Ataxia
Autonomic nervous system (ANS)
Axons
Basal ganglia
Brain stem
Broca's area
Central nervous system (CNS)
Cerebellum
Cerebrum
Computed tomography (CT)
Dendrites
Depolarization
Diffusion tensor imaging (DTI)
Dopamine hypothesis
Electroencephalography (EEG)
Extrapyramidal pathways
Frontal lobe
Functional imaging
Genes
General adaptation syndrome
Glia
Hippocampus
Hypothalamic-pituitary-adrenal (HPA) axis
Hypothalamus
Kindling
Limbic system
Magnetic resonance imagery (MRI)
Magnetic resonance spectroscopy (MRS)
Medulla
Membrane potential
Midbrain
Myelin
Neurogenesis
Neuroimaging
Neuron
Neuroplasticity
Neurotransmitters
Parasympathetic nervous system
Peripheral nervous system (PNS)
Pons
Positron emission tomography (PET)
Reticular activating system
Sensitization
Somatic motor system
Stress-diathesis model
Stressor
Structural imaging
Sympathetic nervous system
Synapse
Temporal lobe
Thalamus
Wernicke's aphasia

Chapter 5

Neurobiologic Considerations in Psychiatric Care

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Introduction

Although the human brain only weighs about 3 pounds, it is composed of approximately 100 billion **neurons** that form intricate communication pathways allowing complex thought, movement, and emotions. It is perhaps not surprising that the neurons, the chemicals that pass between them, and the **genes** that guide them, can at times fail to function properly. Transforming the mental healthcare system into one that is evidence-based requires all health professionals to have an appreciation of the complex biological, psychological and social (biopsychosocial) contributions to mental health and mental illness (Institute of Medicine, 2005). This chapter is intended to provide a basic knowledge of the brain structures and functions, the neurotransmitters and their pathways, and the mechanisms for the development of mental illnesses and disorders and their treatment.

A mnemonic for remembering the 12 pairs of cranial nerves is: "On Old Olympus's Towering Top a Finn and German Viewed Some Hops."

Rapid increases have occurred over the past several decades in the understanding of the neurobiology of mental disorders. New discoveries related to brain physiology, genetic risk factors, and mental illnesses and disorders were reported throughout the 20th century, but especially during the 1990s, a time referred to as the "Decade of the Brain" when the United States Congress provided significant support and funding for brain research. The Surgeon General's Report on Mental Illness (U.S. DHHS, 1999) concluded the decade with a mandate for greater understanding and translation of the neurobiologic underpinnings of mental illness. By 2003, the Human Genome Project (http://genome.gov/HGP/) had mapped the entire sequence of human genes creating databases and improving tools for analyzing the data. With these computerized databases, researchers have been able to study gene sequences and genetic variations associated with psychiatric conditions and behaviors. Vulnerability genes have been identified for most of the mental disorders. The keys to prevention and to new pharmacological and nonpharmacologic treatments for the psychiatric disorders are based upon understanding the interactions between these vulnerability genes and the environment.

The autonomic nervous system (ANS) is responsible for regulation of the organs, glands, and vasculature. The sympathetic and parasympathetic divisions maintain balance, allowing rapid responses to environmental demands, then return to homeostasis.

The Surgeon General's 1999 report at the end of the Decade of the Brain called for more rapid translation of neurobiological research findings into evidence-based treatments for individuals with mental disorders.

The Human Genome Project mapped the entire sequence of human genes by 2003.

Structure and Function of the Nervous System

The central nervous system (CNS) is composed of the brain and spinal cord. The peripheral nervous system (PNS) delivers information to and from the CNS.

The brain and spinal cord make up the **central nervous system (CNS)**. Columns of myelinated **axons** run up and down the spinal cord, delivering information from the periphery to the brain (afferent pathways) and from the brain to the periphery (efferent pathways). The **peripheral nervous system (PNS)** in turn delivers information to and from the spinal cord. **Figure 5-1** shows the divisions of the CNS and PNS. The PNS includes 12 pairs of cranial nerves (with the exception of cranial nerve II, the optic nerve that is part of the CNS; see **Table 5-1** and **Figure 5-2**), 31 pairs of spinal nerves, and two major divisions—the somatic and autonomic nervous systems. The **somatic motor system** is responsible for voluntary control of skeletal muscle. The cell bodies of the neurons that make up the somatic motor system lie within the CNS (in the brain stem or spinal cord), and their axons terminate at neuromuscular junctions. The release of acetylcholine (ACh) triggers contraction of the skeletal muscle. Somatic sensory information from the skin, muscles, and joints enters the spinal cord, and in return, the brain sends commands for voluntary movement.

Traditionally thought of as the involuntary nervous system, the **autonomic nervous system (ANS)** is responsible for the activities of the body that usually take place without conscious guidance—within the internal organs, glands, and vasculature. The two branches of the ANS, the sympathetic and parasympathetic, allow the nervous system to maintain internal balance (homeostasis). In each system, the CNS activates the organs via preganglionic axons that utilize acetylcholine as their neurotransmitter and postganglionic axons that terminate on the effector organs. The postganglionic cell bodies of the ANS lie outside of the CNS either in clusters of cells called ganglia (in the sympathetic nervous system), or on or near the effector organs (in the parasympathetic nervous system). The **parasympathetic nervous system** is responsible for resting functions such as digestion and bowel and bladder function. The vagus nerve (cranial nerve X) provides much of the parasympathetic innervation of the viscera. The remainder comes from the other cranial and sacral spinal nerves. Postganglionic axons in the parasympathetic nervous system also utilize acetylcholine (ACh) as their neurotransmitter. The **sympathetic nervous system** prepares one to fight or flee in an emergency by increasing heart rate and respiratory rate, dilating pupils and bronchi, and stimulating glucose mobilization. Postganglionic axons in the sympathetic nervous system utilize norepinephrine (NE) as their neurotransmitter. Sympathetic activation of the adrenal medulla causes the release

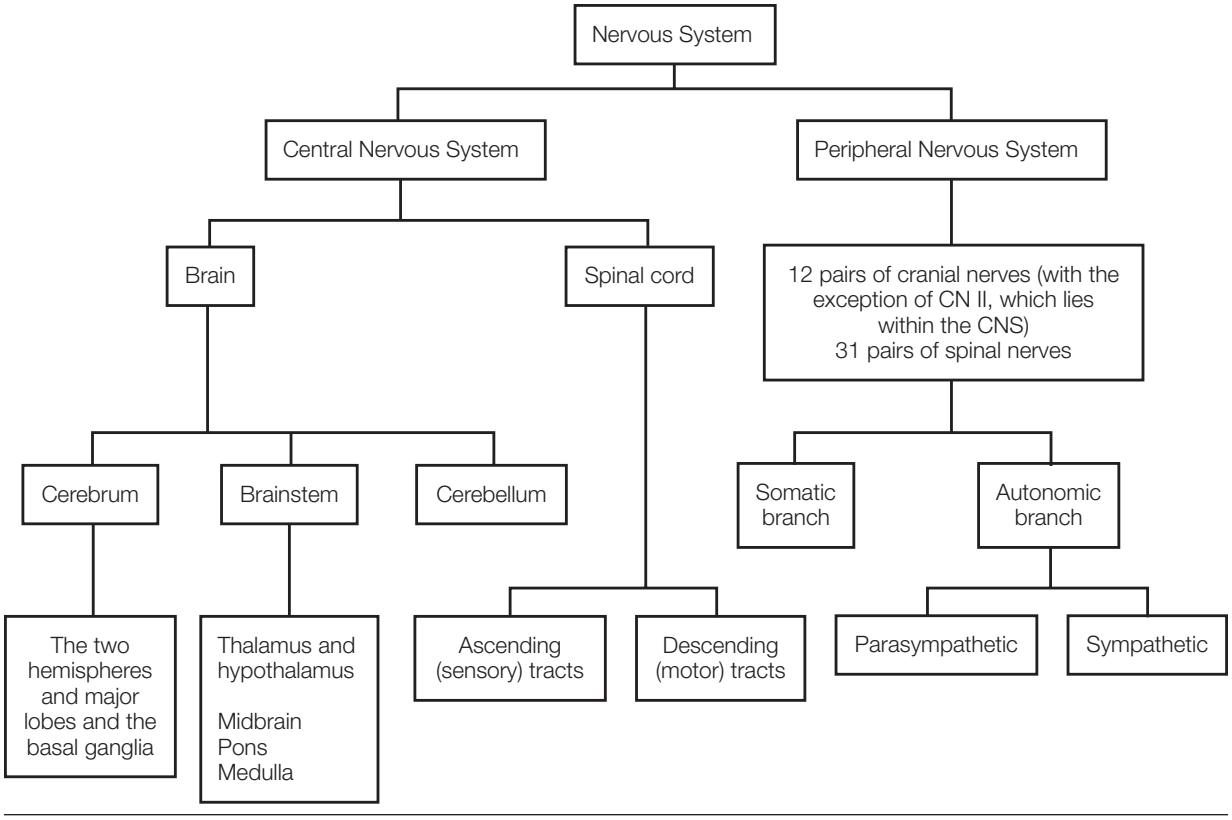

Figure 5-1 Organization of the nervous system.

Table 5-1 The Cranial Nerves

Cranial Nerve	Important Functions
I. Olfactory	Sensation of smell
II. Optic	Sensation of vision
III. Oculomotor	Movements of the eye and eyelid Parasympathetic control of pupil size
IV. Trochlear	Movements of the eye
V. Trigeminal	Sensation of touch to the face Movements of muscles of mastication
VI. Abducens	Movements of the eye
VII. Facial	Movements of muscles of facial expression Sensation of taste in anterior tongue
VIII. Auditory-vestibular	Sensation of hearing and balance
IX. Glossopharyngeal	Movements of muscles in the throat Parasympathetic control of the salivary glands Sensation of taste in posterior tongue Detection of blood pressure changes in the aorta
X. Vagus	Parasympathetic control of the heart, lungs, and abdominal organs Sensation of pain associated with viscera Movements of muscles in the throat
XI. Spinal accessory	Movements of muscles in the throat and neck
XII. Hypoglossal	Movements of the tongue

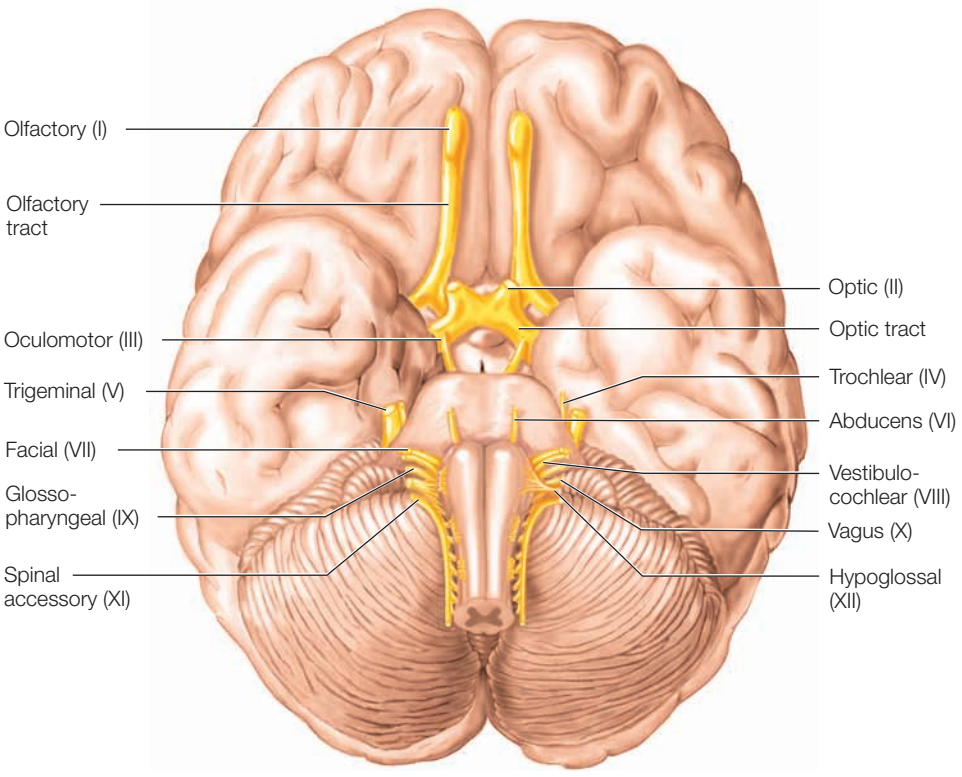

Figure 5-2 The cranial nerves.

of epinephrine (E) (also called adrenaline) into the bloodstream, resulting in a widespread activation. In response to a stressor or threat, the sympathetic nervous system dominates. After the stressor subsides, the parasympathetic system increases in activity and balance is restored. By innervating the same organs, the two opposing systems respond effectively to environmental demands.

In hydrocephalus, CSF builds up, causing the ventricles to enlarge and compress the brain. An increase in ventricular size due to atrophy is not called hydrocephalus.

The CNS is bathed in cerebrospinal fluid (CSF) that flows through the ventricular system and protects the brain from injury. The ventricles of the brain can become enlarged when too much fluid is present (hydrocephalus) or when parts of the brain atrophy, leaving more space for CSF fluid. **Figure 5-3** shows the location of the ventricles of the brain. The CNS can be divided into three major divisions: the cerebrum, the brain stem, and the cerebellum.

Cerebrum

Cerebral Lobes

The **cerebrum** underlies the ability to reason, entertain abstract thoughts, and contemplate concepts like the past and the future, as well as the ability to experience emotions. The cerebrum is the largest portion of the brain and is divided into a left and right hemisphere, each of which contains four major lobes: frontal, temporal, parietal, and occipital (**Figure 5-4**). A fifth area of cortex, called the insula, is less

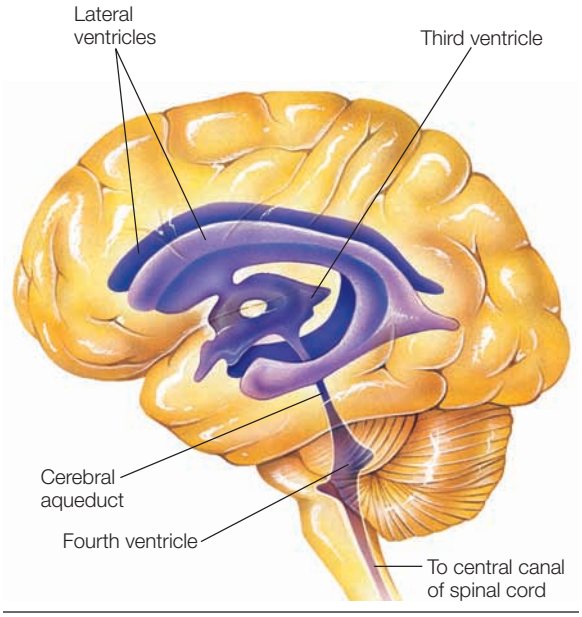

Figure 5-3 The ventricles are filled with cerebrospinal fluid.

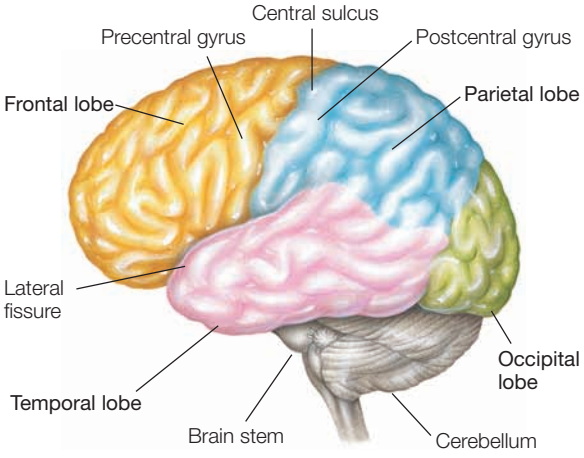

Figure 5-4 **The lobes of the human cerebrum.** The cortex of the brain is identified by gyri (bumps) and sulci (grooves) or fissures (deep grooves).

well known and understood and is not seen from the outer surface of the brain.

Sitting underneath the lobes are several structures referred to as the **basal ganglia**, which means deep nuclei. Together the cerebral hemispheres and basal ganglia are referred to as the "telencephalon." A band of myelinated axons called the corpus callosum connects the two hemispheres, allowing information to pass between them in a unifying manner. The lobes of the brain serve different functions, and so it follows that injury or illness affecting these structures can result in specific alterations in functioning.

Frontal Lobes

The **frontal lobes** of the brain have evolved to be relatively larger in humans than in other species. In human beings, the frontal aspect of the brain, specifically the prefrontal cortex (anterior to the motor cortex), is responsible for executive functioning—planning, organizing, decision making, and working memory (short-term storage and processing of information). While executive functioning takes place in the lateral and upper (dorsolateral) aspects of the prefrontal cortex, other areas control impulses and regulate mood (orbitofrontal) and are involved in reward processing (ventromedial). Together these prefrontal brain areas work with other structures of the limbic system to regulate impulses, emotions, and behavior. The frontal lobes also contain the primary motor, supplementary motor, and premotor cortex and are involved in the interpretation of incoming motor signals and planning and directing of motor responses. Injury to the frontal lobes can affect motor functioning on the opposite side of the body, executive functioning, and short-term working memory. For the majority of people, language functions are located primarily in the left hemisphere, and injury to **Broca's area** (**Figure 5-5**) can cause expressive aphasia, the inability to express oneself with language. The negative or deficit symptoms that we see with some of the psychiatric illnesses may be a reflection of underactivation or underutilization of the frontal executive functions.

The famous story of Phineas Gage helps us understand other functions of the frontal lobes. Gage was a foreman who worked for the railroad system back in the 1800s. One day an accidental explosion blew a tamping iron right through his skull, obliterating a portion of his frontal lobes. He recovered from the accident, but according to his physician, Dr. John Harlow, his personality changed drastically from one of being hard working and easy going to someone who was unmotivated, fitful, irreverent, and grossly profane.

Critical Thinking Question

Can you think of any psychiatric or behavioral disorders associated with impulsivity? Do individuals with these disorders have additional problems with executive functioning?

Temporal Lobes

The **temporal lobes** are especially important in processing auditory information and consolidating long-term memories. Auditory hallucinations, receptive **Wernicke's aphasia** (the inability to understand spoken speech), and difficulty forming new long-term memories may reflect problems with the temporal lobes.

Critical Thinking Question

Can you think of any psychiatric or behavioral disorders associated with impulsivity? How might impulsivity be a risk factor in substance abuse or dependence? Do individuals with these disorders have additional problems with executive functioning?

Two structures that reside within the temporal lobe are the **hippocampus** and the **amygdala**. The

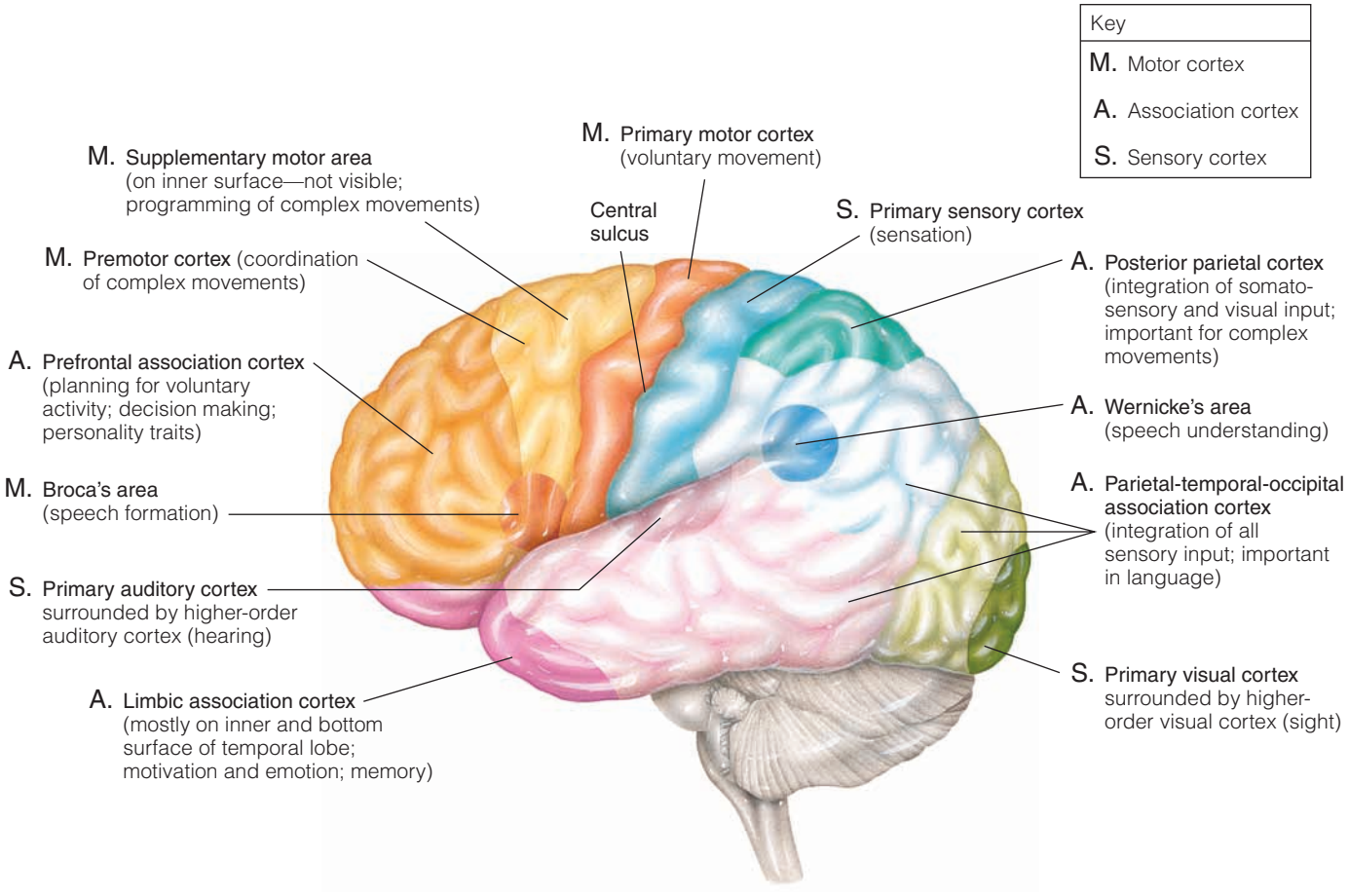

Figure 5-5 **Functional regions of the cortex.** Different functions can be localized to specific areas of the brain. The left hemisphere is dominant for language in the majority of people.

hippocampus, located within the medial temporal lobe, is important in the process of consolidating long-term memories. Without the hippocampus, we would not be capable of storing new information about the facts and events in our lives.

A famous story about a man named Henry Molaison, referred to as "HM," taught us much of what we know today about the functioning of the hippocampal structures. When he was young he had intractable seizures and probably would have died due to complications. In 1953, when he was 23, in an attempt to stop the seizures, surgeons removed both of the anterior portions of his temporal lobes, taking out both hippocampal structures. Following the surgery, HM recovered, and he could recall his life before surgery up to a certain point in time; then his ability to remember just stopped. This type of memory loss is called retrograde amnesia.

The worst problem, however, was that he never again stored or recalled any new facts or events (declarative memories). This type of memory loss is called anterograde amnesia. Dr. Brenda Milner, a researcher at the Montreal Neurological Institute, studied and worked with HM since the 1950s. She introduced herself each time she met him because he had no recollection of ever meeting her. Some types of memory, such as the memory for riding a bike or other skills, are not dependent on the hippocampus. HM improved his skill (procedural memory) at certain activities like table tennis despite not recalling that he had ever played (Milner, 2005). HM died in 2008, but his contributions to neuroscience will live on. Using new methods for three-dimensional digitalized brain modeling, images of HM's brain will soon become available online to neuroscientist researchers worldwide.

The hippocampus is a vulnerable area of the brain. In neurodegenerative illnesses such as Alzheimer's disease, the hippocampus is one of the first areas to show cellular changes and shrinkage. The hippocam-

pus is also vulnerable to chronically elevated levels of circulating cortisol, as might occur in chronic stress-related disorders and depression (Sapolsky, 2003). Unfortunately we cannot avoid stress entirely. The good news is that the hippocampus retains its ability to regenerate neurons throughout life. This process is called **neurogenesis**, and it is facilitated by healthy behaviors such as exercise, good nutrition, and studying for exams!

The amygdala is a small, almond-shaped structure that sits just anterior to the hippocampus in the temporal lobes. The amygdala is very important in relation to stress, serving the function of detecting danger and activating fear and the stress response. Like the hippocampus, the amygdala is important in memory consolidation; however, it specializes in emotional memories and appears to be an essential locus for the storage of fear-related memories (Schafe, Doyere, & LeDoux, 2005). Although it is extremely rare, individuals who do not have either amygdala cannot recognize negative emotion in others. The rare Kluver-Bucy syndrome demonstrates this phenomenon. When the anterior portions of the temporal lobes are removed through disease or injury, individuals display diminished fear and aggression, a tendency to identify objects by oral examination rather than visual inspection and inappropriate sexual behavior.

For most of us, our amygdalas are present bilaterally, yet we all differ in sensitivity. Like a thermostat, some people seem to be able to take quite a lot of threat before triggering the stress or fear response system, whereas others appear to be extremely sensitive and hypervigilant. It is likely that a combination of genes and environmental experiences determines the level of sensitivity. Fortunately, both antidepressants and psychotherapy can reduce the sensitivity and reactivity of the amygdala.

Parietal Lobes

The parietal lobes contain the primary sensory cortex, which receives afferent sensory information about touch, pain, temperature, and proprioception (limb location), and the sensory association cortex where these signals are analyzed and interpreted. When the parietal lobes are injured or lesioned, such as can happen with a cerebrovascular accident, individuals may develop sensory and perceptual problems such as perceptual abnormalities of body image and spatial relationships—even the full neglect of one side of the body. Complex motor movements are coordinated between the frontal lobe (planning and motor) and the parietal lobe (sensory and limb position). A selective inability to perform learned purposeful movements (**apraxia**) or identify objects (agnosia) may suggest parietal injury. Agnosias are defined by their functional deficits; for example, asterognosia refers to the inability to identify objects by touch (e.g., a key in one's pocket), a skill that requires intact sensory perception.

Occipital Lobes

The occipital lobes house the primary and association visual cortices, areas specialized in receiving visual signals and interpreting visual stimuli. Injuries or damage to the occipital cortex can result in vision changes and problems recognizing and interpreting visual information.

Basal Ganglia

The basal ganglia are a collection of neurons deep in the cerebrum. They consist of three major structures that cover the thalamus in each hemisphere: the caudate, putamen, and globus pallidus. Together the caudate and putamen are sometimes referred to as the "striatum." In psychiatric nursing and psychopharmacology, you will hear terms that refer to the basal ganglia. The pyramids refer to the bundles of descending corticospinal motor axons that mostly cross over (decussate) at the level of the medulla. **Extrapyramidal pathways** are motor pathways that are outside of the medullary pyramids. Whereas the pyramidal motor pathways are responsible for voluntary skilled movements, the extrapyramidal system provides support for movement through control of posture and muscle tone and initiation of movement, and it is importantly regulated by the basal ganglia.

When you hear of the extrapyramidal symptoms that include bradykinesia, tremor, and dystonia, what medical condition do you think of? If you thought of Parkinson's disease, you were right. One of the extrapyramidal pathways is a dopamine pathway that travels from the substantia nigra (dopamine producing cells in the midbrain) to the striatum (of the basal ganglia). We refer to that pathway as the nigrostriatal pathway. *Nigro* tells you the origin of the pathway and *striatal* tells you the destination. In Parkinson's disease, the dopamine-producing cells in the substantia nigra degenerate, decreasing the dopamine that is available in the basal ganglia for initiation of

movement. Extrapyramidal side effects or EPSs are common in individuals who are taking the first-generation, conventional, antipsychotics that are potent dopamine D2 receptor antagonists. EPSs resemble a Parkinson's-like condition that is reversible once the dopamine receptor antagonism is reduced in the nigrostriatal pathway.

One of the most important functions of the basal ganglia is to facilitate the initiation of willed movements, such as walking or writing.

Brain Stem

The **brain stem** consists of the central structures that sit below and support the cerebrum. The body's vital functions depend on neuron clusters within the brain stem. Also, located within the brain stem is an area called the **reticular activating system** (RAS), whose function seems to be keeping us conscious and awake. Damage to this area of the brain stem can result in a sleeplike state of coma. The brain stem initiates a number of protective, automatic motor behaviors such as maintaining balance, blinking, and head movements.

Thalamus and Hypothalamus

At the superior aspect of the brain stem lie the thalamus and hypothalamus, together referred to as the "diencephalon." Inside the **thalamus** are the major input and output relay nuclei that interact with every portion of the brain. Nerve impulses do not enter or exit the conscious brain without going through the thalamus. The thalamus sorts, amplifies, directs, and integrates sensory information.

The **hypothalamus** lies inferior to (beneath) the thalamus and superior to (above) the pituitary gland, where it helps maintain homeostasis by regulating vital functions, including body temperature, blood glucose level, salt and water balance, and our biologic clock. The hypothalamus is the major control center for the pituitary gland and is central in coordinating the physiological response to detected threats or stress via the **hypothalamic-pituitary-adrenal (HPA) axis**. Axons from the hypothalamic neurons release their neurotransmitters into the portal circulation of the anterior pituitary, influencing the release of pituitary hormones that act on the gonads, thyroid glands, adrenal glands, and mammary glands (**Figure 5-6**).

Midbrain

Clusters of cell bodies that produce monoamine neurotransmitters reside within the **midbrain**, also referred to as the "mesencephalon." The midbrain is the origin of several of the diffuse regulatory pathways of the brain. The cluster of cell bodies that produces norepinephrine is collectively referred to as the "locus coeruleus." The cluster that produces

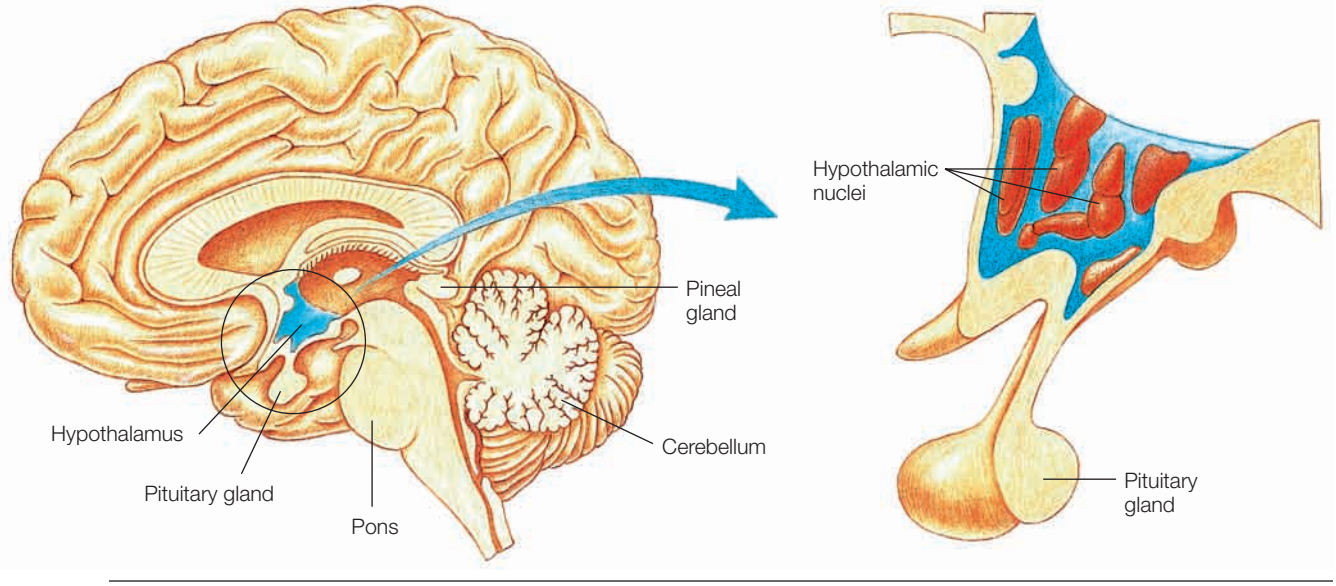

Figure 5-6 The hypothalamus is the master gland of the endocrine system.

dopamine is referred to as the "substantia nigra." The pathways are named by their origin and termination within the brain, so by knowing that *meso* refers to the mesencephalon, you would know that a mesolimbic pathway travels from the midbrain to the limbic structures of the brain.

Critical Thinking Question

Name the origin and the destination of the following pathways of the brain: (1) corticospinal, (2) spinothalamic, and (3) Nebraska Avenue. Just kidding on number 3. However, sensible naming strategies for pathways make it easier to find your way around the brain than around most cities!

Pons

Not only does the **pons** contain important neurotransmitter-producing cell bodies, but it also is a very important conduit for the ascending and descending pathways that pass between the cerebrum and cerebellum. Scattered groups of cell bodies referred to as the "raphe nuclei" produce serotonin in the midbrain, pons, and medulla.

Medulla

The descending corticospinal tracts cross (decussate) at the level of the **medulla**. This results in the right motor cortex controlling the muscles on the left side of the body and the left motor cortex controlling the muscles on the right side. The crossover accounts for how a cerebrovascular accident in one hemisphere of the brain creates functional difficulty for the other side of the body. The bundles of myelinated axons that course through the medulla are sometimes referred to as the "pyramids." The bundles of axons that lie outside of the pyramids are extrapyramidal pathways.

Cerebellum

Bundles of axons travel between the pons and the **cerebellum**, providing a means for the cerebellum to communicate with the rest of the central and peripheral nervous systems. The cerebellum smoothes out and coordinates the sequence of muscle contractions that are necessary to control movements. Individuals with cerebellar damage will have difficulty touching a finger to their nose or moving an arm to point from one location in space to another. Such an individual might also need to walk with a wide-based gait. The term **ataxia** refers to these uncoordinated and inaccurate movements. Acute and chronic abuse of substances such as alcohol can result in cerebellar dysfunction and ataxia.

Cellular Mechanisms of Communication

The Cells of the Brain

There are two main types of cells in the nervous system: the **glia** and neurons. The most abundant are the glial cells, which provide support and protection to the neurons. Bear, Connors, and Paradiso (2007) use the analogy of a chocolate chip cookie to describe the relationship between neurons and glia. The chips (neurons) are surrounded and supported by the more plentiful dough (glia). In early development, the glial cells also provide the structures upon which the neurons can migrate, with the help of neurotrophic (brain growth) factors, to appropriate sites in the brain. There are five identified types of glial cells. The oligodendroglia form myelin sheaths around the axons in the CNS, just as Schwann cells do in the PNS. The astrocytes provide physical support to the neurons and protect them by regulating extracellular levels of ions and neurotransmitters, such as potassium and glutamate. Microglia are macrophages that play an important role in the brain's immune system. In response to pathogen invasion or tissue damage, they promote an inflammatory response that engages the immune system to initiate tissue repair. The ependymal cells line the fluid-filled ventricles of the brain. Although we tend to think of neurons as being the most important cells in the brain, without glial cells they could not function. Indeed, Einstein's brain was found to have more glial cells relative to neurons in the posterior parietal cortex than a control population (Diamond, Scheibel, Murphy, & Harvey, 1985).

The neuron is the basic functional unit of the brain for information processing. Neurons have three distinct parts—the cell body (soma), **dendrites**, and axon (see **Figure 5-7**). Central to the soma is the nucleus that contains the DNA, the set of genetic instructions that guide development and functioning. The DNA determine the type, production, and distribution of proteins within the neuron and the functioning of the cell. Outside of the nucleus, within the cytoplasm of the soma, are several organelles that

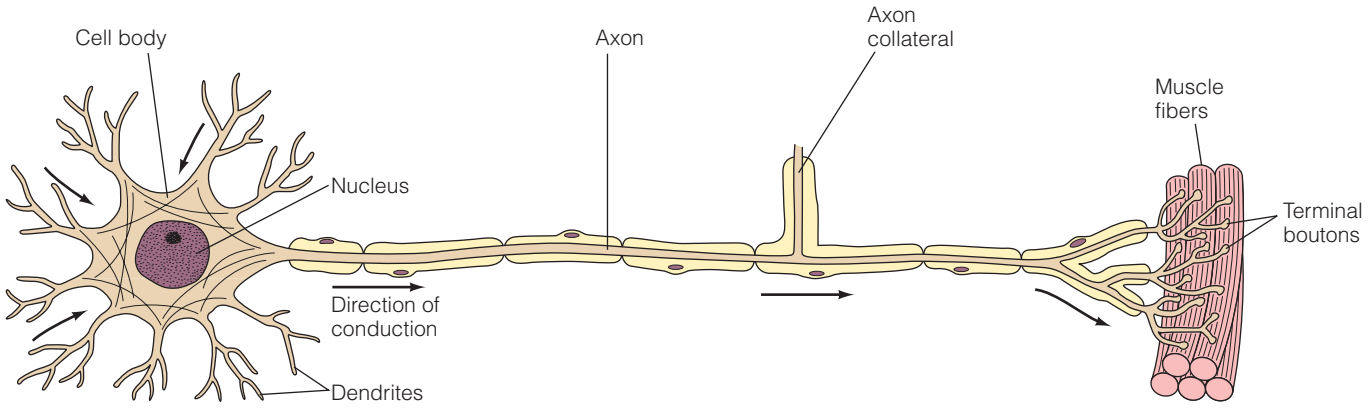

Figure 5-7 **A prototypical neuron.** Neurons are distinguished from other cells in the body by their dendrites and axons. Their terminals (sometimes called boutons) typically form synapses with the dendrites of other neurons, but may synapse on cell bodies or axons. This figure shows the axon terminating at the neuromuscular junction of skeletal muscle fibers.

serve specific functions in the manufacture of important proteins. Ribosomes are the sites of protein synthesis; Golgi bodies cleave proteins into smaller functional units; and mitochondria produce the energy, adenosine triphosphate (ATP), needed for all cell activity. The proteins produced by neurons are transported to sites within the neuron where they serve as enzymes, receptors, ion channels, transport pumps, peptide neurotransmitters, and membrane and structural proteins.

Dendrites and axons distinguish the neuron from other cells in the body. The dendrites receive chemical signals from other neurons, and the axons conduct electrical signals (action potentials) to their terminals that result in the release of chemical messengers (neurotransmitters), which activate the dendrites and cell bodies of other neurons. A gross inspection of the brain reveals both gray and white matter. The gray matter consists of the cell bodies and other nonmyelinated structures such as glia. The white matter is named for the white appearance of myelinated axons. Axons that are insulated with myelin sheaths are able to conduct the electrical signals more quickly and efficiently, with the axon potential jumping from one break in the **myelin** (also referred to as a "node of Ranvier") to the next (**Figure 5-8A**).

Critical Thinking Question

Multiple sclerosis is a disease characterized by the destruction of myelin. Based on your knowledge of the function of myelin, what symptoms would you expect?

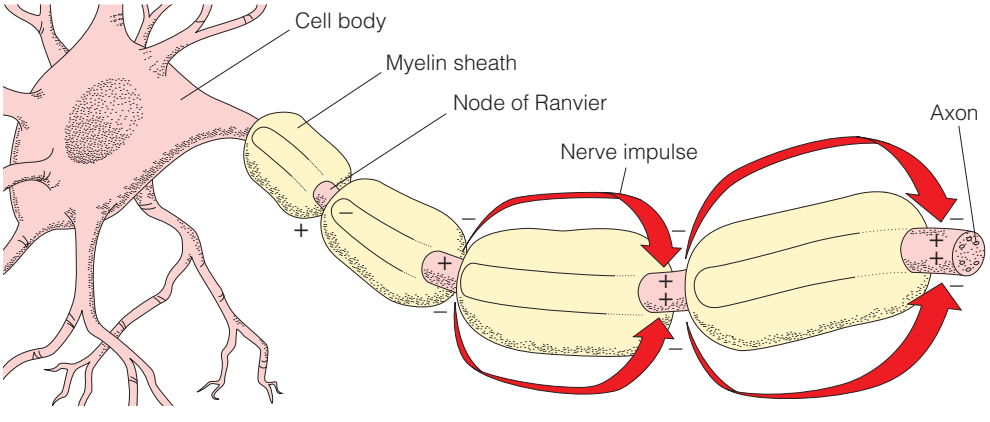

Figure 5-8A **Neurotransmission.** An electrical signal is conducted down the axon to the terminal.

Neurotransmitters

Large peptide **neurotransmitters** (e.g., beta-endorphins) are produced in the soma and transported to the terminals for release. Smaller amine and amino acid neurotransmitters are produced in the axon terminals and packaged into tiny synaptic vesicles. Neurotransmitters are released into the synapse upon the arrival of electrical signals (action potentials). **Figure 5-8B** depicts the arrival of an action potential at the terminal triggering the release of neurotransmitter from the vesicles. The neurotransmitter diffuses across the synapse and engages the receptors on the postsynaptic membrane. Notice the abundance of mitochondria in the terminal area indicating the great energy needs for the processes of neurotransmission, including reestablishing the membrane potential, transporting neurotransmitters back into the terminal, and repackaging them in vesicles.

Most notable to the etiology and treatment of mental illnesses are the **amine neurotransmitters**: acetylcholine (ACh), serotonin (5HT), dopamine (DA), and norepinephrine (NE). The family of neurotransmitters called catecholamines refers to dopamine, norepinephrine, and epinephrine, all synthesized from a common amino acid precursor called tyrosine. See **Table 5-2** for a list of the common neurotransmitters and their functions. Clusters of cells that produce these neurotransmitters are located in the midbrain, pons, and medulla and send their axons into many areas of the cerebrum. The result is that the neurotransmitter pathways are distributed throughout the brain and have widespread regulatory effects on brain activity. In addition, areas of the brain are connected via circuits for regulation of various functions.

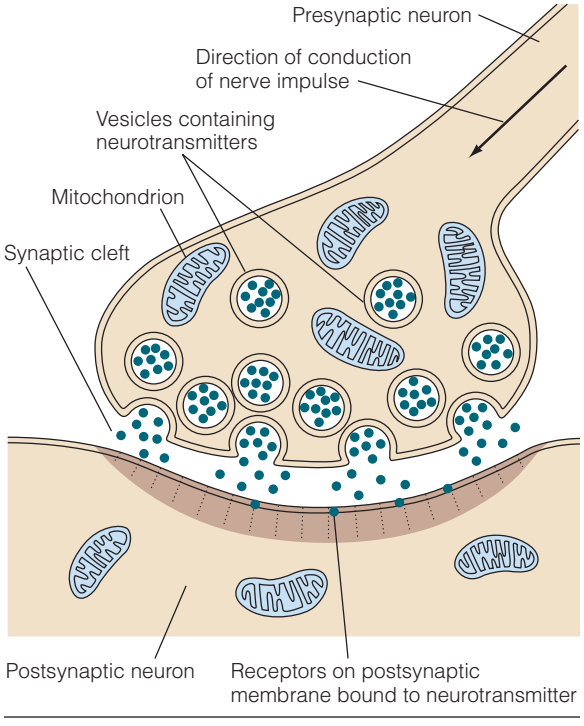

Figure 5-8B A chemical signal is released into the synapse.

Synapses

A synapse is the region of contact between neurons where information is transferred.

Although it might appear that neurons are part of one vast continuous network, they are actually separated from one another by small spaces called **synapses**. Upon the arrival of electrical signals (action potentials), chemical signals (neurotransmitters) diffuse across synapses from presynaptic terminals to postsynaptic receptors. The neurotransmitters do not actually pass into the postsynaptic cells. Instead, like keys, they activate receptors on postsynaptic membranes and then float back into the synapse where they await their fate. Some neurotransmitters float away, others are broken down by enzymes in the synapses, and the rest are pumped back into the terminal. Once in the terminal, the neurotransmitters may be broken down by enzymes (e.g., monoamine oxidase) or repackaged into vesicles for recycling. Note that several familiar psychotropic medications target the pumps (e.g., serotonin reuptake inhibitors) and the enzymes (e.g., monoamine oxidase inhibitors).

Neurotransmitters and their receptors mediate psychiatric disorders and are targets for psychopharmacologic interventions.

Critical Thinking Question

Depression is thought to be related to diminished levels of serotonin and other monoamine neurotransmitters. How would you explain the mechanism of action of fluoxetine (Prozac) to a client?

Each neurotransmitter has several receptor types, and each given receptor type may have multiple subtypes with different actions. Thus, one neurotransmitter can cause multiple actions in different areas of the brain. Neurotransmitters are messengers that activate receptors. Some receptors are actually ion channels that open up rapidly in response to the neurotransmitter, allowing charged ion molecules to flow into or out of the postsynaptic cell. Receptors that open an ion channel are called ligand gated or inotropic. Others use a second messenger on the inside

Neurotransmitters are chemical "messengers" that activate specific receptors.

Table 5-2 Major Neurotransmitters in Mental Health and Illness

Chemical Classification	Neurotransmitter and Receptor Types	Major Pathways and Sites of Action	Normal Functions and Dysfunctional Symptoms in Mental Disorders
Amine	Dopamine (DA) Five major receptor types with multiple subtypes: D1, D2, D3, D4, D5 The term *catecholamine* describes DA, NE, and E. NE is synthesized from DA and E is synthesized from NE.	Mesocortical: ventral tegmental area (VTA) to prefrontal cortex.	Cognition and executive functioning. Deficits: cognitive (negative symptoms), decreased information processing.
		Mesolimbic: VTA to limbic areas of brain.	Emotion regulation: motivation, pleasure, reward. All drugs of abuse increase DA in this pathway. Deficits: reduced motivation, positive affect, joy, interest, pleasure; increased apathy, anhedonia. Excesses: drug craving, positive symptoms of psychosis, increased goal-directed behaviors in mania.
		Nigrostriatal: Substantia nigra to basal ganglia.	Part of the extrapyramidal system that controls movement. Deficits: bradykinesia, tremor, dystonia, akathisia in disorders such as Parkinson's disease, and EPS of dopamine antagonist medications. Excesses: dyskinesias, tics.
		Tuberoinfundibular: Hypothalamus to anterior pituitary.	Inhibits prolactin. Risk of galactorrhea with dopamine receptor antagonist (antipsychotic) therapy.
Amine	Norepinephrine (NE) Two major receptor types with multiple subtypes: alpha and beta NE is converted to epinephrine (E) in the adrenal medulla. E is also known as adrenaline.	Locus coeruleus to prefrontal cortex.	Concentration, working memory, speed of information processing. Deficits: decreased alertness, cognitive dysfunction.
		Locus caeruleus to limbic system, especially the amygdala and its projections.	Mood regulation. Deficits: reduced positive affect, loss of energy, psychomotor retardation. Excesses: anxiety, panic, hypervigilance, psychomotor agitation.
		Postganglionic neurons of the sympathetic nervous system.	Participates in the regulation of the autonomic nervous system. In response to stress, facilitates fight or flight. Excesses: symptoms of activation without corresponding stressor (e.g., increased heart rate, blood pressure, respiratory rate).
		Adrenal medulla releases E into the bloodstream in response to stress.	E is involved in the coordination of the visceral response to stress.
Amine	Serotonin (5HT) At least seven major receptor types with multiple subtypes: 5HT1–5HT7	Raphe nuclei to prefrontal cortex and limbic system.	Mood regulation. Deficits: increased negative affect, depressed mood, guilt, worthlessness, suicidal ideation, disgust, fear, anxiety, hostility, irritability, loneliness, impulsivity.
		Raphe nuclei to basal ganglia.	Deficits: worry, apprehensive expectation, obsessions. Excesses: side effects of SSRIs may include Parkinsonism or akathisia from excess inhibition of dopamine (5HT normally inhibits DA).
		Raphe nuclei to hypothalamus.	Regulation of appetite and eating behavior. Dysregulated in eating disorders and depression.
		Raphe nuclei to brain stem regulatory centers and spinal cord.	Stimulation of specific 5HT receptors with SSRIs or other serotonergic medications may result in gastrointestinal symptoms, nausea, sleep disturbances, and sexual dysfunction.

Table 5-2 Major Neurotransmitters in Mental Health and Illness *(Continued)*

Chemical Classification	Neurotransmitter and Receptor Types	Major Pathways and Sites of Action	Normal Functions and Dysfunctional Symptoms in Mental Disorders
Amine	Acetylcholine (ACh) Two major receptor types with multiple subtypes: muscarinic and nicotinic	Brain stem nuclei and Meynert's nucleus to hippocampus, amygdala, and throughout the cortex.	Critical role in memory and higher cortical executive functions such as learning, problem solving, and judgment. Deficits resulting in learning and memory problems in cognitive decline, Alzheimer's dementia, and excessive medication-induced anticholinergic states.
		Other sites of cholinergic-producing neurons include all motor neurons in the spinal cord and brain stem.	Causes contraction of skeletal muscle. Deficits result in muscle weakness (e.g., myasthenia gravis).
		ACh is the preganglionic neurotransmitter of sympathetic and parasympathetic neurons and the postganglionic neurotransmitter of parasympathetic neurons.	Effects on cardiac muscle: ACh slows heart rate. Parasympathetic ACh activity facilitates digestion, growth, immune responses, and energy storage. Activity of the parasympathetic nervous system is generally reciprocal to activity in the sympathetic system.
Amino acids	Glutamate Four major receptor types: NMDA, AMPA, kainite, and metabotropic	Synthesized from glucose and other precursors in all cells.	Serves as an excitatory neurotransmitter throughout the brain. Plays a key role in long-term potentiation, memory formation, and synaptogenesis. The NMDA receptor is thought to mediate normal excitatory neurotransmission by opening positively charged calcium ion channels leading to rapid depolarization of postsynaptic cells. Excitotoxicity: too much glutamate lets in too much calcium, which results in excess free radical formation and eventual death of the neuron. This is thought to be a mechanism in neurodegenerative disorders. Less toxic increases in glutamate may be related to other positive symptoms such as anxiety, panic, psychosis, and mania.
	Gamma-aminobutyric acid (GABA) Two major receptor types with several subtypes: GABA A and GABA B	Synthesized from glutamate in neurons that use it as a neurotransmitter. It is not one of the 20 amino acids used to make proteins.	Serves as an inhibitory neurotransmitter by allowing negatively charged chloride to enter, reducing the chances that a neuron will fire. Deficits in GABA inhibitory activity have been linked to anxiety disorders and insomnia. Excessive inhibitory activity can result in sedation, ataxia, and memory disturbance.

Source: Adapted from Stahl (2008).

of the postsynaptic membrane to cause a cascade of chemical changes, eventually even influencing the expression of the genes that guide the cellular functions. The receptors that use a second messenger are called G-protein or metabotropic receptors. G-protein receptors have slower, longer-acting, modulating effects.

Let's look at glutamate as an example. Glutamate has four identified receptors (see Table 5-2). Three of the receptors are linked to ion channels and create rapid changes in the postsynaptic cell: NMDA (N-methyl d-aspartate), AMPA (amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), and KAR (kainate). The NMDA receptor mediates normal

excitatory neurotransmission. Too much glutamate action at NMDA receptors may eventually be excitotoxic to the cells and may be part of the mechanism of neurodegeneration in illnesses such as Alzheimer's disease. The fourth glutamate receptor is a metabotropic receptor that uses a second messenger system. The NMDA is implicated in the creation of lasting changes in synapses, a process called long-term potentiation (LTP), as well as in excitotoxicity (the death of cells due to too much glutamate letting too much calcium into cells). LTP is thought to be a key neuroplastic change in the brain involved in forming long-term memories. Although the complexity of neurotransmitter–receptor actions is enormous, new receptor subtypes are continually being discovered, and as they are, newer drugs can be designed that have more specificity and fewer side effects. Memantine, an NMDA glutamate receptor antagonist medication, holds promise for reducing the excitotoxic effects of excessive glutamate and is being used to decrease the rate of neurodegenerative processes in individuals with Alzheimer's disease.

Neurotransmission

Due to a combination of diffusion and electrical factors, the inside of resting neurons is more negatively charged than the outside, polarized at about –65 millivolts. The separation of charge between the outside and the inside of the neuron is referred to as the **membrane potential**, and it is largely maintained by the sodium-potassium pump drawing potassium into the neuron and sodium out—both against their concentration gradients. A great deal of cellular energy (adenosine triphosphate or ATP) is required to maintain the difference in potential. Because ATP is manufactured from oxygen and dietary sources of energy, when oxygen is lacking the pumps fail and the neurons can no longer function, resulting in brain damage within four minutes.

Neuroplasticity describes the dynamic nature of the brain and its functions that permit humans to adapt to environmental changes, learn, and remember.

The membrane potential is the separation of charge between the outside and inside of the neuron.

Neurogenesis is the birth of new neurons.

When an action potential arrives in the presynaptic terminal, it causes a brief **depolarization** (a shift in the charge towards 0 millivolts and above) of the membrane potential due to a rapid influx of positively charged calcium ions, the calcium in turn triggering the release of neurotransmitter into the synaptic cleft. Following depolarization, the cell quickly repolarizes so that it can be ready to respond to the arrival of the next action potential. So now imagine thousands of axon terminals releasing neurotransmitters into the synaptic clefts of the dendrites or the cell body of a single neuron. The neurotransmitters may be excitatory (like glutamate) or inhibitory (like gamma-aminobutyric acid—GABA). If the neurotransmitter is excitatory, it causes positively charged sodium or calcium to flow into the postsynaptic neuron, depolarizing it and shifting the charge toward the threshold for firing an action potential. If the neurotransmitter is inhibitory, it causes negatively charged chloride to flow into the postsynaptic neuron, resulting in the cell becoming negatively charged (returning the cell toward its resting potential and less likely to fire off another action potential. Small currents build and move along the dendrites toward the cell body. Between the cell body and the axon is an area called the axon hillock, somewhat like a toll booth on a highway. If there is enough currency (depolarization) to pay the fare (shifting the charge from –65 millivolts to a threshold level of about –50 millivolts), then an all-or-none action potential is generated and it travels down the axon. If there is not enough depolarization at the axon hillock, the cell does not fire. The frequency and pattern of action potentials is like a Morse code of the brain, transmitting information to be processed and interpreted.

Neuroplasticity

The ability that we have to adapt to environmental changes, learn, and remember reflects the amazing **neuroplasticity** of the brain. It is difficult to imagine how complex thoughts, feelings, and behaviors emerge from small electrical and chemical signals in the brain. Neuroplasticity describes the dynamic nature of the brain and its functions. We now know that new cells are born (neurogenesis) throughout one's lifetime. A peak number of synapses is present around age 6, followed by a period of extensive pruning and increased efficiency. Long-term potentiation or strengthening of synapses builds our memories. Long-term depression or weakening of synapses helps us forget. Receptors are up regulated or down regulated depending on the availability and need for specific neurotransmitters. When a neurotransmitter is deficient, the receptors up regulate in an attempt to compete for more of the neurotransmitter. Likewise, when a medication increases the levels of a neurotransmitter, the receptors down regulate to decrease the overload. Feedback loops to the nucleus assure that cells are always responding to ever-chang-

ing environmental demands. Because the brain has so much plasticity in the early years, children have more capacity than adults to compensate for major brain injuries. Individuals who keep their brains active in later life through physical exercise and cognitive activities show continual neurogenesis and may have more of a buffer against neurodegenerative processes and dementia.

Two important processes involving neuroplasticity have recently been implicated in the development of psychiatric disorders: disturbances in myelination and energy metabolism. Myelination of brain pathways is a developmental process that continues for several decades after birth. Because of this, myelination of brain neurons is thought to be influenced by factors such as levels of environmental enrichment and neuronal activity. Deficits in myelin formation or demyelination may lead to disruptions in functional connectivity between brain regions and impaired cognitive functioning. New research evidence suggests that the impaired cognitive functioning seen in a variety of psychiatric conditions reflects myelin abnormalities (Assaf & Pasternak, 2008; Fields, 2008). Mitochondria, the energy-producing organelles in neurons, have also been found to play important roles in neuroplasticity and cellular resilience, including neurogenesis, the growth of axons and dendrites, and synaptic changes. Disturbances in mitochondrial energy metabolism have been implicated in several neurodegenerative and psychiatric disorders, including Alzheimer's dementia, bipolar disorder, and schizophrenia (Clay, Sillivan, & Konradi, 2010).

The limbic system regulates emotion, learning, and memory.

Regulation of Emotion

The Limbic System

The **limbic system** describes several structures that function as a system to regulate emotion, behavior, memory, and learning. **Figure 5-9** depicts the major structures together with their connections—the frontal cortex, thalamus, hypothalamus, cingulate gyrus, hippocampus, amygdala, and mammillary bodies. The limbic system is crucial to our motivation and important in producing behaviors that are critical to the survival of the species, such as behaviors that foster appropriate social interactions and success in producing offspring. Love and desire arise from this system, as well as fear and paranoia. Memory for the events of our lives and the emotional texture is what helps us make decisions and plan for the present and future. Mental disorders involve dysregulation of the limbic system.

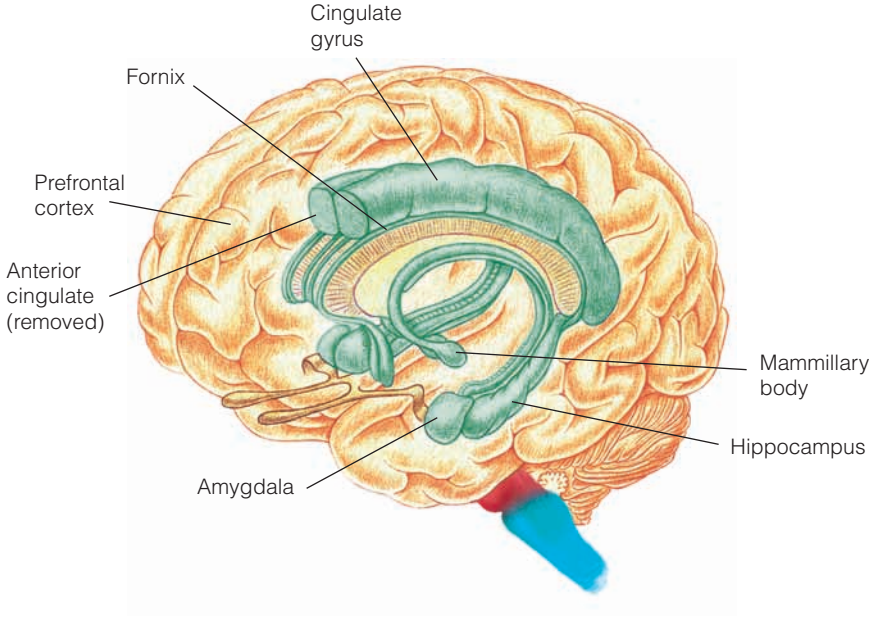

Figure 5-9 **The limbic system.** The limbic structures form a ring around the thalamus and hypothalamus (not shown). The structures and their connecting pathways (e.g., the fornix) are involved in the regulation of emotion and memory.

The Stress Response

The modern-day concept of stress is influenced by the work of Hans Selye and the publication of his theory of **general adaptation syndrome (GAS)**. In his publication, *The Stress of Life* (1956), Selye identified three stages in the human response to stressors. In the first, the alarm stage, an individual becomes aware of the stress or stressor and the sympathetic nervous system springs into a fight-or-flight reaction. In the second stage, resistance, the body attempts to adapt to the stress response, and in many instances adaptation occurs. If homeostasis is not restored, the third stage is that of exhaustion, where the body can no longer respond to the stress and over time may develop illnesses or die. Selye conceived of the response as nonspecific—in other words, the same response regardless of the type of stressor or the individual.

Selye's general adaptation syndrome model did not account for individual differences in stress reactivity. We now know that the stress response is triggered when an individual perceives that the demands of a situation outweigh his or her capacity to adapt. What might be fun to some people (e.g., skydiving) is experienced as frightening and stressful to others. Some people seem more naturally resilient to stressors and demonstrate less reactivity than others. Genetic contributions as well as life experiences probably account for these differences.

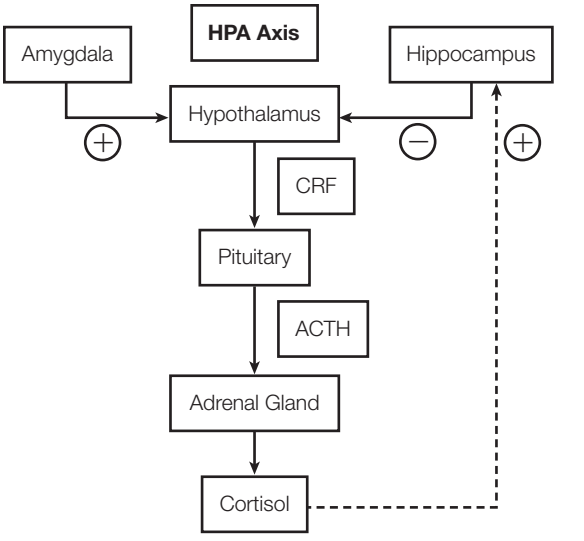

Figure 5-10 **The HPA axis.** In response to stress, neurons in the hypothalamus release a peptide neurotransmitter called corticotrophin-releasing hormone (CRH) into the blood of the pituitary circulation, triggering the release of adrenocorticotrophic hormone (ACTH) into the general circulation. ACTH triggers the release of cortisol from the adrenal cortex. Amygdala activation stimulates the HPA axis and hippocampal activation suppresses it.

Acute Stress

Chronic stress, such as that experienced by individuals living in poverty or with illness, is characterized by elevated levels of cortisol and its physiological correlates.

A stressor (acute or chronic) is anything that threatens the body's homeostasis.

A **stressor** is anything that threatens homeostasis. Potential stressors may be acute physical challenges, such as hunger, cold, restraint, chemicals, shock, surgery, and bodily injuries, or psychological challenges, such as adversity, emotional illness, financial hardships, work issues, social hierarchy conflicts, and neglect. Our bodies are well adapted to dealing with acute stressors. The stress response is characterized by the activation of two major stress pathways: the **hypothalamic-pituitary-adrenal (HPA) axis**, yielding increases in the glucocorticoid called cortisol (**Figure 5-10**), and the sympathetic nervous system (SNS), yielding increases in the catecholamines norepinephrine (NE) and epinephrine (E). Cortisol increases the availability of blood glucose for energy and suppresses the immune system. The catecholamines sharpen the attention and activate the cardiovascular system to increase blood flow to the large muscles (for fighting or fleeing). If acute stress continues, short-term reversible impairments in memory may occur. Once the stressor is avoided or dealt with effectively, homeostasis is restored and digestion, growth, and other resting functions return.

Chronic Stress

Unfortunately, humans have many more things to worry about than being chased by predators and fighting or fleeing. Instead, we are bombarded by constant mild to major stressors. In addition, a large portion of our population suffers from the chronic stress of low socioeconomic status—poverty, hunger, manual labor, sleep deprivation, and low levels of personal control. Others are threatened by neglect or abuse, domestic or community violence, or even war. Persistent activation of the stress response appears to be a risk factor for the development of physical illness as well as depression and anxiety disorders. Although the fight-or-flight response may subside, the HPA axis remains overactive and neurotrophic factors such as brain-derived neurotrophic factor (BDNF) may be reduced. Hippocampal neurons are especially vulnerable to the chronically elevated levels of glucocorticoids and include a metabolic

syndrome characterized by elevated blood pressure, increased abdominal fat, and elevated blood sugar (Kyrou, Chrousos, & Tsigos, 2006; Sapolsky, 2005). Whereas elevated levels of glucocorticoids (cortisol) decrease inflammation with acute stress, excessive exposure over prolonged periods has been linked to a deteriorated immune response accompanied by neuroinflammation (Sorrells, Caso, Munhoz, & Sapolsky, 2009). Furthermore, excessive glucocorticoids may lead to reductions in astrocytes and resultant increases in glutamate, leading to excitotoxicity and neuronal damage or death (Rajkowska & Miguel-Hidalgo, 2007). These studies have linked neurodegenerative changes to the effects of chronic stress.

McEwen (2001) refers to the process of maintaining stability or homeostasis through adaptation as "allostasis." **Allostatic load** is the wear and tear produced by the repeated activation of allostatic (adaptive) mechanisms. He identifies four types of allostatic load: (1) repeated challenges/chronic stress, (2) failure to habituate with repeated challenges, (3) failure to shut off the response after the challenge is past, and (4) failure to mount an adequate response. Developmental or environmental determinants of differences in allostatic load can include early stressful life experiences resulting in increased reactivity of the HPA axis function and increased sensitization to later stress exposure (Charney, 2003; Heim, Newport, Mletzko, Miller & Nemeroff, 2008), and stressful adult experiences that cause lasting changes in HPA functioning (Mason et al., 2001).

Stress is relevant to all of the psychiatric disorders, first because of its potential role in their etiology and maintenance, and second because of the chronic stress of living with mental disorders. Stress also contributes to the development, maintenance, and outcome of substance use disorders by increasing drug cravings, altering subjective responses to alcohol, and increasing alcohol consumption. Fortunately the effects of stress can be prevented or reversed through primary (e.g., education) and secondary (screening) prevention efforts.

Mental Disorders

Gene and Environmental Influences

Are mental disorders inherited? The answer is yes, at least partially. Genetic factors provide the vulnerability or risk for mental illness but they do not explain the whole picture. Consider the case of two identical twins (monozygotic) who share the same genes but are discordant for an identified mental disorder. In monozygotic twins, concordance is thought to reflect genetic vulnerability, and discordance is thought to reflect the environmental contribution to mental disorders. All of the mental disorders have been found to show some degree of discordance. Reviews of twin studies indicate that the heritability is highest for schizophrenia (82–85%) (Kendler, 2001), bipolar disorder (85%) (Bienvenu, Davydow, & Kendler (2011), autism spectrum (80%) (Lichtenstein, Carlstrom, Rastam, Gillberg, & Anckarsater, 2010), attention-deficit/hyperactivity disorder (ADHD) (79%) (Lichtenstein et al., 2010), and Alzheimer's dementia (75%) (Bienvenu et al., 2011); it is midlevel for alcoholism (52–58%) (Kendler, 2001) and lowest for the anxiety disorders (28–53%) (Bienvenu et al., 2011; Kendler, 2001) and major depression (29–52%) (Kendler, Gatz, Gardner, & Pedersen, 2006).

Allostasis is the process of maintaining stability or homeostasis through adaptation.

Genome-wide analyses are being used to identify disorders. Genetic researchers are also attempting to identify the epigenetic and environmental risk factors. Epigenetic refers to the study of reversible changes in gene function that occur without a change in the DNA sequence. Environmental factors may influence the epigenetic processes to switch genes on or off. Therefore epigenetic research is also seeking more knowledge on how to reverse the environmental and epigenetic contributions to the development of mental disorders.

The **stress-diathesis model** describes the environmental interaction in mental disorders. Diathesis refers to the genetic predisposition or vulnerability, and stress describes the contribution of environmental factors. Environmental contributions to the development of mental illness may occur in utero, as in the case of one fetus getting more oxygen or more of a virus than the other. They may also stem from childhood experiences. Individuals who have experienced early childhood stress, such as the loss of a parent, neglect, or abuse, are much more vulnerable to depression and anxiety disorders later in life. Stress may also trigger the earlier onset of a mental disorder such as schizophrenia or bipolar disorder. In addition, severe or chronic stress in adulthood is associated with vulnerability to anxiety and mood disorders. Finally, individual differences contribute to the environments in which individuals choose to live, so genes affect the environment and the environ-

The stress-diathesis theory explains the development of psychiatric disorders as a combination of diathesis (genetic predisposition) and environmental stress.

Genetic factors provide the vulnerability or risk factors for an individual to develop a mental illness, but they do not explain the whole process.

ment affects the gene expression, perhaps through changes in epigenetic factors.

The following content discusses the current theories of etiology for a sample of mental disorders. The most recent neurobiological discoveries far outpace the development of new drugs for treatment. For each disorder, the interrelated and overlapping theories of etiology illuminate the complexities of gene–environment interactions and challenge our current diagnostic categories of the mental disorders.

SSRIs inhibit the pumps that transport serotonin back into the presynaptic terminal, resulting in an increase in available serotonin in the synapse.

Mood Disorders

Unipolar Depression

Depression appears to be related to a depletion of monoamine neurotransmitters such as serotonin, norepinephrine, and dopamine.

Sadness and grief are normal responses. Prolonged periods of sadness or anhedonia (lack of pleasure) accompanied by other physiological symptoms such as appetite and weight changes, sleep disruption, fatigue, and psychomotor agitation or retardation are not normal. Persons with these symptoms are experiencing depression, a serious yet common illness. Findings from the Global Burden of Disease Study (World Health Organization, 2008) indicate that depression is the third leading cause of disability worldwide and the first in middle- and high-income countries, creating an enormous burden for society.

The vulnerability to depression is heritable. Children of parents who have had depression have a higher risk for depression than their counterparts, yet early life stressors such as the loss of a parent, neglect, or abuse can predispose a person to the development of depression even without an obvious family history of depression (Gutman & Nemeroff, 2003; Heim et al., 2008). In addition, the illness is not the same for every person. Approximately half of individuals with depression have elevated levels of cortisol, suggesting a prolonged stress response (Lee, Ogle, & Sapolsky, 2002). These individuals may show a prolonged response to the dexamethasone suppression test, demonstrating a weakened ability to shut down cortisol activity in the body. Prolonged elevation of cortisol is toxic to the neurons of the hippocampus, the area of the brain involved in long-term memory consolidation.

Monoamine oxidase inhibitors (MAOIs) block the enzyme MAO from destroying monoamine neurotransmitters, allowing them to accumulate in the presynaptic cell.

Depression appears to be, to some extent, due to a depletion of monoamine neurotransmitters such as serotonin, norepinephrine, and dopamine. The exact mechanism for this is unclear; however, one possibility is that an enzyme that metabolizes monoamines is elevated, leading to lower than normal levels (Meyer et al., 2006). The monoamine reduction hypothesis is supported by the observation that antidepressants effectively reduce depression, and all antidepressants increase the availability of monoamine neurotransmitters. However, individuals differ in their responsiveness to antidepressants. Some individuals with depression respond best to antidepressants that specifically target the serotonin system (e.g., selective serotonin reuptake inhibitors or SSRIs). Others do best with antidepressants that target the serotonin and norepinephrine systems (e.g., serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclics), and others do best with antidepressants that target the dopamine system (e.g., bupropion). Approximately 30% of depressed patients fail to go into remission with antidepressant treatment (Caraci, Copani, Nicoletti, & Drago 2010).

Finally, late-life (after age 50) depression is a risk factor for the development of Alzheimer's disease. Studies suggest that both disorders are associated with neuroinflammation and impairments in neurotrophic (brain growth factor) signaling. Chronic inflammation may be associated with neurodegenerative changes and the development of dementia (Caraci et al., 2010; Hashioka, McGeer, Monji, & Kanba, 2009). Antidepressants decrease brain inflammation and increase the release of neurotrophic factors, so they are somewhat protective, and researchers are developing new drugs to target these pathways.

Critical Thinking Question

Antidepressants increase the availability of monoamine neurotransmitters almost immediately. Why, then, does it take 3–6 weeks to achieve therapeutic reductions in depression? This is a very difficult question, and no one knows for sure; however, think through some of the neuroplastic changes or brain adjustments that take place over time. For example, consider the up-regulation of monoamine receptors that might occur in depression and the readjustment that might need to take place in recovery.

Bipolar Disorder

Bipolar disorders are characterized by the occurrence of manic (bipolar I) or hypomanic (bipolar II) episodes. Most individuals who have experienced manic episodes will also experience depressive epi-

sodes. Dr. Robert Post and his colleagues (Post et al., 2003) at the National Institute of Mental Health (NIMH) have spent years trying to identify the neurobiologic underpinnings of bipolar illness and have come up with two descriptive concepts—sensitization and kindling. **Sensitization** describes the tendency for initial mood episodes to be linked to identified stressors, but later episodes require less of a stressor or none at all. People seem to become sensitized to the episodes themselves, such that the occurrence of mood episodes increases the risk for future episodes. **Kindling** is a term used to describe the lowered threshold for setting off neuronal activity in seizure disorders. Manic episodes are like seizures in that they result from too much neuronal activity, something like a limbic-lobe seizure. Support for this model is gained from the observation that antiseizure drugs are effective in treating and preventing manic episodes. Lithium and the mood stabilizers appear to stabilize the neuronal membrane, making it less sensitive and increasing the threshold for activation. Bipolar depression may be treated with antidepressants; however, mood stabilizers are generally given concurrently to prevent swings from depression into mania.

Specific brain structural changes associated with bipolar disorder are reduced anterior cingulate volume (part of the limbic system that is important in directing attention), early-onset white matter (myelin) abnormalities, and, less consistently, reduced hippocampal volume and enlarged ventricular volume. Behavioral changes that might be accounted for by the structural changes are deficits in attention (anterior cingulate) and deficits in learning and memory (hippocampus). Prefrontal cortex abnormalities are suggested by abnormalities in the reward system of the brain, with a decreased responsiveness during periods of depression and an increased responsiveness during periods of mania. NIMH researchers Hasler, Drevets, Gould, Gottesman, and Manji (2006) suggest that these brain changes may be mediated by interactions among hypercortisolemia, glutamate neurotoxicity, and stress-induced reduction in neurotrophic (brain growth) factors.

Anxiety

Anxiety can be a symptom, a syndrome, or a disorder. As a symptom, anxiety and its stronger variant, fear, constitute the emotional component of a stress response. When the stress response is activated by a perceived threat, the sympathetic fight-or-flight response is accompanied by anxiety or fear. The main neurotransmitters involved in the sympathetic fight-or-flight response are the noradrenergic (NE) and adrenergic transmitters (E). Aside from anxiety, other symptoms of norepinephrine (noradrenergic) and epinephrine (adrenergic) activation include tachycardia, tremor, and sweating.

Anxiety can also be part of a syndrome, associated with other disorders such as substance intoxication or withdrawal or medical problems. The *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (*DSM-IV-TR*; APA, 2000) lists anxiety as a part of a syndrome of intoxication for alcohol, amphetamine, caffeine, cannabis, cocaine, hallucinogens, inhalants, and phencyclidine, and of withdrawal for alcohol, cocaine, sedatives, hypnotics, and anxiolytics. In addition, anxiety is a common symptom associated with numerous over-the-counter and prescribed medications, including bronchodilators, corticosteroids, sympathomimetics, and thyroid preparations. All of these conditions and medications have the activation of the CNS in common.

The treatment of choice for anxiety as a symptom or as part of a syndrome is generally a sedative-hypnotic, like a benzodiazepine, which quiets down the CNS by enhancing the inhibitory activity of GABA. Other drugs are also used, depending on the target symptoms. Beta-blockers and other antihypertensives (e.g., clonidine) may be used to decrease the peripheral symptoms of tremor or behavioral activation but are less powerful in blocking the subjective and emotional aspects of anxiety.

Finally, anxiety can be a mental disorder. The *DSM-IV-TR* anxiety disorders include panic disorder, simple phobia, social phobia, obsessive compulsive disorder (OCD), acute stress disorder, posttraumatic stress disorder (PTSD), and in children, separation anxiety disorder. The neurobiologic mechanisms for the anxiety disorders are more complex, and treatment is not simply aimed at decreasing sympathetic activity or increasing inhibitory activity. Two overlapping neurobiologic brain regions and circuits that are implicated in the primary symptoms of anxiety include the amygdala (anxiety or fear), and the cortex-basal ganglia circuit (worry and obsessions) (Stahl, 2008). Many neurotransmitters are involved in regulating these two circuits, and any or all may be involved in anxiety disorders. Potential neurotransmitter abnormalities include excessive cortisol from

Anxiety can be a symptom, a syndrome, or a mental disorder.

dysregulation of the HPA axis, too much excitatory (glutamate) activity, too little inhibitory activity (GABA), or dysregulation of any of the monoamine neurotransmitters. In chronic anxiety, serotonergic dysregulation seems to be an important contributor, because the SSRI antidepressants are the first line of treatment. Consider the following two examples of anxiety OCD and PTSD.

In individuals with OCD, approximately 50% do not respond to the SSRIs alone (Stahl, 2008), implying that serotonin dysregulation cannot be the only explanation. OCD shares similarities with other disorders that involve the dopamine pathways of the basal ganglia: Tourette's disorder and pediatric autoimmune neuropsychiatric disorders associated with streptococci (PANDAS) (Snider & Swedo, 2003). These disorders tend to be associated with movement irregularities or tics involving too much dopamine and OCD symptoms. Treatment with neuroleptics (dopamine antagonists) decreases both the tics of the body and the tics of the mind. Individuals with OCD who do not respond to SSRIs alone are often treated with the addition of a neuroleptic. Taken together, these findings suggest that OCD may be a disorder involving dysregulation of serotonin and dopamine in the basal ganglia and its connections.

Posttraumatic stress disorder (PTSD) is a response to severe environmental stress, such as might be produced by sexual or physical abuse or military combat. PTSD has become a national concern now that 23.7% and 30.5% of active duty and National Guard troops, respectively, meet *DSM-IV-TR* criteria for PTSD at 12 months postdeployment from a war zone, and 7.3% and 11.3% have serious functional impairment (Thomas et al., 2010). The symptoms of PTSD include persistent reexperiencing of a traumatic event, persistent avoidance of stimuli associated with the event, and persistent symptoms of increased arousal. Each of these symptoms may have a different neurobiological mechanism. Persistent intrusive thoughts and reexperiencing may result from an inability of higher cognitive structures to repress negative emotional memories. Avoidance symptoms of PTSD are thought to result from conditioned fearlike encoding of the environment surrounding a traumatic event. Hyperarousal and hypervigilance may result from hyperactivity of the amygdala and noradrenergic signaling. Finally, the HPA axis is also affected; however the evidence suggests that, in contrast to healthy participants and those with major depression, cortisol concentration may be decreased in the plasma of persons with PTSD (Martin, Ressler, Binder, & Nemeroff, 2010).

In summary, an individual's perception of threat and feelings of fear and anxiety are associated with the amygdala and its activation of the stress response pathways (1) from the locus coeruleus to the sympathetic nervous system's release of norepinephrine and epinephrine, and (2) from the hypothalamus to the adrenal gland's (HPA axis) production of cortisol. Under normal conditions, once the stressor is gone, homeostasis is restored. Under chronic stress conditions, however, balance is not restored. Heightened peripheral sympathetic nervous system arousal may persist, especially in panic disorder. The HPA axis may continue unabated, releasing CRH, ACTH, and cortisol, especially during the anticipatory anxiety of a panic disorder and in avoidance of situations associated with phobias (Martin et al., 2010).

Critical Thinking Question

What stress management techniques do you use to reduce your own stress levels? Do you think that stress management should only be in the treatment plan of individuals with anxiety disorders? If not, why?

Schizophrenia

Schizophrenia involves both neurodevelopmental and neurodegenerative processes.

Schizophrenia, the most common psychotic disorder, generally gets diagnosed as a person reaches one's late teens or early 20s, at a time when the prefrontal portions of the brain are completing their migration, connections, and pruning. The course of schizophrenia can be described by both neurodevelopmental and neurodegenerative changes. Critical gene–environment exposures that may increase the risk for schizophrenia include advanced paternal age, intrauterine adversities such as fetal hypoxia, maternal stress or illness, postnatal brain injuries and illnesses, and severe early life trauma (Perrin, Kleinhaus, Messinger, & Malaspina, 2010). As the normal brain develops after birth, the maximum numbers of synapses are formed by around the age of 6 years, and after that a preprogrammed process of pruning takes place, ultimately making the brain more efficient. In schizophrenia, faulty migration and misalignment of neurons are suggested by early developmental delays in motor, cognitive, and social/

emotional functioning. The brains of children and adolescents with schizophrenia also show enlarged ventricles and decreased gray matter maturation compared to their healthy age-matched peers (Rapoport, Addington, Frangou, & MRC Psych, 2005). This finding suggests that the cortical matter either has not developed as much compared to normal peers or was excessively pruned.

Structural scans of adults with schizophrenia show ventricular enlargement (indicating smaller brains), medial temporal lobe volume reductions (hippocampus), and frontal lobe volume reductions (Ross, Margolis, Reading, Pletnikov, & Coyle, 2006). Dysfunction of the prefrontal cortex is apparent on tasks of working memory and executive functioning.

Psychotic disorders such as schizophrenia are diagnosed by the presence of positive symptoms of hallucinations, delusions, disorganized speech, or disorganized behavior. For over 50 years, the **dopamine hypothesis** of schizophrenia has been a guiding framework in understanding the disease. The hypothesized mechanism for the positive symptoms involves excessive amounts of dopamine in the limbic system. Support for this hypothesis comes from the efficacy of dopamine antagonists in reducing positive symptoms.

Dopamine antagonists do not reduce the negative symptoms (e.g., affective flattening, alogia, and avolition) of schizophrenia. The conventional antipsychotics are especially strong antagonists of one of the dopamine receptors, called the D2 receptor. D2 antagonism in the dopamine pathways that terminate in the prefrontal cortex (involved in executive cognitive functioning) may even worsen negative symptoms. This is because dopamine is an important neurotransmitter in mediating motivation and higher level cognitive functioning. Fortunately, the newer atypical antipsychotics (serotonin-dopamine antagonists) spare dopaminergic functioning in the prefrontal cortex through the relation between serotonin and dopamine. The result is that with atypical antipsychotic treatment, individuals may experience decreases in both the positive and negative symptoms of schizophrenia.

Extrapyramidal Side Effects

EPS can occur as a result of treatment with conventional antipsychotics, and the nurse may be the first healthcare practitioner to identify and treat the symptoms. To understand the potential EPS, it is useful to know that there are four major dopaminergic pathways, named by their origin and terminus, in the brain:

1. The mesocortical pathway goes from the mesencephalon (another name for the midbrain) to the frontal cortex.
2. The mesolimbic pathway travels from the midbrain to the limbic system.
3. The nigrostriatal pathway travels from the substantia nigra in the midbrain to the striatum (the basal ganglia) and is involved in movement.
4. The tuberoinfundibular pathway travels from the hypothalamus to the infundibulum (the stalk) of the anterior pituitary.

We have already discussed the hypothesis that, in schizophrenia, dopamine is elevated in the mesolimbic pathway and deficient in the mesocortical pathway. But what about the other two pathways?

The nigrostriatal dopaminergic pathway is not usually affected by schizophrenia itself; however, when the pathway is blocked by a conventional antipsychotic, movement-related EPS can result. Bradykinesia, tremors, and dystonias are all possible antipsychotic-induced symptoms of Parkinsonism. Akathisia is severe restlessness. Another less common EPS side effect is lactation, which is caused by the antagonism of D2 receptors in the tuberoinfundibular pathway.

It is important for nurses to understand that the EPS are side effects and not changes in the psychotic disorder, and that they can be treated and reversed. The best practice today is to avoid the EPS by using an atypical antipsychotic as a first-line agent. If the conventional agents are used, it may be necessary to add another medication such as an anticholinergic, antihistamine, benzodiazepine, beta blocker, or alpha adrenergic antagonist to reduce the side effects. Abnormal movements should be closely monitored for early intervention and evaluation of outcomes. The Abnormal Involuntary Movement Scale (AIMS; National Institute of Mental Health, 1975) is an excellent tool for that purpose. Treatment compliance is essential to recovery, and nurses are often the first healthcare practitioners to notice and report changes in functioning or condition.

The dopamine hypothesis of schizophrenia cannot explain all of the symptoms, nor can it explain the neurodevelopmental and neurodegenerative aspects of the disorder. Recent theories implicate glutamate, microglia, and myelin. A hypothesis of glutamate hy-

pofunction and impaired glutamate NMDA receptor functioning in the pathophysiology of schizophrenia is supported by the observation that phencyclidine (PCP), an NMDA receptor antagonist, mimics the positive symptoms seen in schizophrenia. Glutamate insufficiency may be especially detrimental to hippocampal functioning and memory consolidation (Tamminga, Stan, & Wagner, 2010). Microglia are part of a neuroinflammatory process in the brain. Prolonged microglia activation may produce proinflammatory cytokines and free radicals, leading to neurodegenerative changes including neuronal death (apoptosis), atrophy, and increased ventricular size (Monji, Kato, Kanba, 2009). A myelin dysfunction hypothesis is supported by volume reductions in white matter and impaired functional connectivity. Impaired cognitive functioning in schizophrenia is probably more detrimental to overall functioning and recovery than the positive symptoms (Fields, 2008).

Dementia

Dementia is the loss of memory and cognitive abilities. The most common cause is Alzheimer's disease.

Dementia is the loss of memory and cognitive abilities. The most common cause of dementia is Alzheimer's disease (AD). In the U.S., approximately 15% of persons over the age of 70 have dementia, 10% due to dementia of the Alzheimer's type (Plassman et al., 2007). Other forms include vascular dementia, frontotemporal dementia, Pick's disease, and Lewy body dementia. Dementia is also common in Parkinson's and Huntington's disease. A score of 25 or below on the Mini-Mental State Evaluation (Folstein, Folstein, & McHugh, 1975), or similar measure, can alert the psychiatric nurse that a patient needs further evaluation for possible dementia.

Alzheimer's Disease

Alzheimer's disease progresses slowly and is often mistaken for normal cognitive changes of aging until later in its course. Although a definitive diagnosis cannot be made without an autopsy, the diagnosis may be given once a person manifests multiple cognitive deficits including memory impairment and cognitive disturbances (e.g., aphasia, apraxia, agnosia, executive deficits). Neuroimaging might reveal enlarged ventricles indicating brain atrophy. Microanatomical changes include accumulation of a protein called beta amyloid in the neurons, and neurofibrillary tangles created by clumps of structural components of the cell called microtubules. Needless to say, neurons that become stuffed with plaques of protein and tangles of microtubules are unable to perform their normal functions and eventually die.

Early on in the progression of the disease, acetylcholinesterase inhibitors can be prescribed to slow the metabolism of acetylcholine, improving its availability for learning and memory. Later on, glutamate antagonists may slow the progressive neurodegenerative processes. But nothing has been found to halt disease progression entirely, and, with or without treatment, it continues to destroy brain function. Fortunately, new research is addressing how we might someday be able to target the beta amyloid gene precursors to prevent amyloid plaques and other cellular changes.

Substance Disorders

The *DSM-IV-TR* (APA, 2000) lists substance-specific diagnostic criteria for 11 classes of substances. The *DSM-IV-TR* does not include the term *addiction*, referring to the loss of control over the use of a substance; rather, it defines substance abuse, dependence, intoxication, and withdrawal patterns. What seems remarkable is that although the substances can have strikingly different acute effects, they share the characteristic of being rewarding to the user, a quality that promotes repeated drug use, and in vulnerable individuals, the loss of control in limiting intake. Over time, behavior can change to compulsive drug seeking, loss of control, and the emergence of negative emotional states that reflect a motivational withdrawal syndrome when access to the drug is prevented. Koob & Volkow (2010) describe drug addiction as a progressively pathological cycle composed of three interacting stages, each with separate brain circuits: binge/intoxication; withdrawal/negative affect; and preoccupation/anticipation (craving). Impulsivity driven by the positive consequences of drug taking dominates at the early stages, and compulsivity, driven by the negative reinforcement of taking away withdrawal symptoms or stress, dominates in the later stages. Successive neuroadaptations are what shift impulsive drug use into compulsive use and eventually a chronic and relapsing condition.

Binge/intoxication stage. Drugs of abuse cause different acute effects. Nicotine activates cholinergic nicotinic receptors. Alcohol and sedatives enhance GABA inhibition. Marijuana and opiates interact

with the brain's own cannabinoid and opiate receptors. Amphetamines enhance norepinephrine and dopamine. Hallucinogens enhance serotonin. In the end, through their connections with dopaminergic cells, all drugs of abuse activate the mesolimbic reward system. The dopamine-producing neurons have their cell bodies in the ventral portion of the midbrain, and their axons terminate in a location rich with cell bodies of other neurons, called the nucleus accumbens (NA) located in the basal ganglia. Drugs that rapidly increase brain dopamine are especially rewarding. The reinforcing effects of drugs may also involve other neurotransmitters such as glutamate and brain opioids. The resultant development of drug habits involves the basal ganglia.

Withdrawal/negative affect stage. Koob and Volkow (2010) report that all drugs of abuse are associated with a motivational withdrawal syndrome characterized by negative mood states and sleep disturbances. This is not the same as the physical withdrawal syndrome that differs with each drug. As a consequence of chronic drug use, the brain adapts by down-regulation of dopamine receptors and by decreasing baseline levels of dopamine, having the unfortunate result of decreasing sensitivity to normally rewarding activities like food or sex. Decreased sensitivity to dopamine may result in tolerance as it takes more of the drug to have the same effect. Neural adaptations in other brain circuits occur as well. Chronic drug use appears to activate the amygdala and the HPA axis during withdrawal, resulting in fear, negative mood states, and stress.

Preoccupation/anticipation (craving). In addition, increased sensitivity to drug-related cues (such as seeing the place where drugs were previously purchased or used) and impairment in the executive functioning of the frontal cortex can lead individuals to become less able to inhibit sudden urges and actions related to drug seeking and taking. Enhanced sensitivity to stress, as well as relevant to changes in the HPA axis and cortisol receptors, may increase the tendency to focus on drug-related cues. Glutamate may also contribute to the learning of drug cues (conditioned responses).

Obviously not everyone who uses a drug becomes addicted or dependent. Drug addictions are the result of complex gene-environment interactions. Individual risk factors may include genetic vulnerability, sensitivity to environmental stressors and rewards, drug availability, adolescence, overall impulsivity, and mental illness. The first step towards treating substance disorders is to understand that the complex neuroplastic changes in the brain are long lasting and that recovery takes time and patience. Treatment should include strategies that enhance the salience of natural rewards, strengthen inhibitory control and executive function, decrease drug cues and conditioned responses to them, and improve mood if disrupted (Volkow & Li, 2005).

Neuroimaging

There are many ways to image the brain, but to date none of them provides definitive diagnoses for mental disorders (**Table 5-3**). **Neuroimaging** has played an important role in expanding our knowledge base related to the structure, function, and neurochem-

Table 5-3 Neuroimaging: What it Measures

Structural	Functional	Other
Computed Tomography (CT): Anatomical image	Functional MRI (fMRI): Change in blood flow related to neural activity	Magnetic Resonance Spectroscopy (MRS): Metabolic or chemical concentrations
Magnetic Resonance Imaging (MRI): Anatomical image	Positron Emission Tomography (PET): Cerebral blood flow and cerebral glucose metabolism	Electroencephalogram (EEG): Surface scalp electrical activity
Diffusion Tensor Imaging (DTI): White matter tract orientation	Single-photon Emission Computed Tomography (SPECT): Cerebral blood flow and glucose metabolism	

istry of the CNS. Two categories of brain imaging may be used—structural imaging and functional imaging. **Structural imaging** with **computed tomography (CT)** and **magnetic resonance imaging (MRI)** gathers information regarding the physical constitution of the brain at any one point in time. These techniques are helpful in detecting structural changes that may result from injury or disease of the brain. The results are not dependent on thought, motor activity, or mood. **Functional imaging**, not surprisingly, tells us about the functioning of the brain. The two most common techniques for examining function are **positron emission tomography (PET)** and functional magnetic resonance imaging (fMRI). These methods detect changes in regional blood flow and metabolism during thought, motor activity, or mood changes.

Clinical indications for imaging in clients with psychiatric disorders are listed in **Table 5-4**. Although the neuroimaging of the brain provides important diagnostic clues that may be helpful in formulating a diagnosis, many of the findings are nonspecific, showing only ventricular enlargements or generalized atrophy, and the techniques are expensive to perform. These procedures are not routinely used in clinical practice; however, with the rapid advances in technology, they have been extremely helpful in expanding our understanding of the neurobiology of psychiatric disorders. Psychiatric neuroimaging continues to evolve in methodologies, techniques for analysis, and clinical utilization.

Structural Imaging

In CT, thin slices or tomographic images of the brain are obtained by X-ray, reconstructed, and entered into a computer. With this technology, a variety of views of the brain can be produced, revealing the gross organization of the gray and white matter and the position of the ventricles. CT is superior to MRI for assessing calcification, acute hemorrhage, and bone injury and is also less expensive and more readily available than MRI. CT studies in persons with schizophrenia have shown enlargement of ventricles and structural alterations in prefrontal and medial temporal areas.

MRI uses radio waves and magnets to obtain images. Since both white and gray matter in the brain have different densities of hydrogen ions, they respond differently to perturbations of a strong magnetic field. As a person rests quietly, the MRI scanner passes an electromagnetic wave (radio signal) through the head while it is positioned between the poles of a large magnet. When the magnetic fields are shifted, the movement of the hydrogen ions is detected and a detailed image of the whole brain, both gray and white matter, is obtained. MRI is superior to CT and generally is the preferred modality when assessing for subcortical lesions, demyelination, and lesions near bone. **Figure 5-11** shows how follow-up MRIs have been used to detect schizophrenia-related brain changes over time.

The advantages of MRI over CT for structural imaging are that it does not require x-irradiation, the image is more detailed, and the computer can construct brain slices in any plane desired. The disadvantages are that it is difficult for individuals to lie still for the approximately 20 minutes that it takes to do an MRI, and some individuals feel frightened by the close proximity of the scanner and the loud noises that it emits. Fortunately, many sites now offer open MRIs that are not as confining. With MRIs, measurement of reduced hippocampal volumes has been reported in multiple studies of depression, bipolar disorder, PTSD, and dementia.

Table 5-4 Clinical Indications for Structural Imaging

Acute change in mental status (affect, behavior, or personality) plus one of the following:
• Age greater than 50
• Abnormal neurological examination
• History of significant head trauma
• New onset psychosis
• New onset delirium or dementia of an unknown cause

Source: Dougherty & Rauch (2008). Guidelines for the use of MRI of the brain in psychiatric populations.

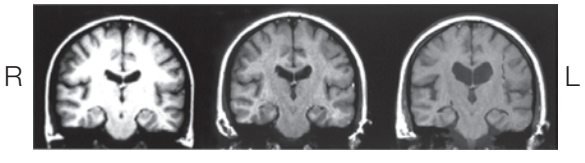

Figure 5-11 An MRI shows progressive atrophy and increased ventricular size in the same female with schizophrenia. She was 34 years-old at the time of the 10 year follow-up.

Magnetic resonance spectroscopy (MRS) relies on the magnetic principals of MRI and is used to detect chemical and metabolic information in certain brain areas. The data are depicted as a spectrum. For example, investigators can detect a chemical that corresponds to neuronal health called NAA. Reductions in NAA can indicate areas of neuronal degeneration. With MRS imaging, comparisons can be made of the concentrations of substances between healthy brains and brains with neuropsychiatric abnormalities. Recent discoveries implicate the use of MRS as a sensitive diagnostic tool that assists with earlier diagnosis of dementia through the measurement of decreases in NAA and increases in another chemical, myoinositol (Mountford, Stanwell, Lin, Ramadan, & Ross, 2010).

Diffusion tensor imaging (DTI), an MRI-based technology that enables visualization and characterization of white matter pathways, has now become one of the most popular neuroimaging methods in brain research. DTI is based upon the observation that the motion or diffusion of water molecules in the brain is faster along white matter fibers than it is perpendicular to them. The difference between the motions (parallel vs. perpendicular), referred to as "anisotropy," is the basis of DTI. Abnormalities in white matter pathways have been identified in all of the psychiatric disorders that are characterized by cognitive deficits, including schizophrenia, Alzheimer's dementia, bipolar disorder, OCD, autism, and attention-deficit/hyperactivity disorder (ADHD). These findings support the hypothesis of functional disconnectivity between brain areas; however, the white matter changes do not identify specific patterns associated with specific psychiatric disorders, so they are not diagnostic (Assaf & Pasternak, 2008; Fields, 2008).

Critical Thinking Question

What will you teach a client regarding the potential limitations from an MRI related to a diagnosis of mental illness?

Functional Imaging

Functional imaging gives us a sense of what is going on in the thinking, living brain. With functional imaging, we are able to see which areas of the brain are active during certain types of mental tasks and how brain activation and metabolism changes as a result of brain lesions or mental illness. As with other neuroimaging methods, the information is not diagnostic because of the considerable overlap in abnormalities of the limbic structures in mental disorders. Functional imaging has been used extensively in psychiatric research to help further our understanding of functional deficits and pharmacological therapies in clinically defined patient groups. When the brain is active it utilizes more oxygen and glucose (recall that these are needed to make cellular ATP energy) and more blood is sent to the active regions. Both the functional magnetic resonance imaging (fMRI) and the positron emission tomography (PET) scan can detect changes in regional blood flow and metabolism within the brain.

For a PET scan, an individual lies in the scanner, and a radioactive solution is injected intravenously. The emitted radiation is used to recreate a 3D image of the brain. As the individual performs a task such as thinking of a series of numbers, blood flow and metabolism increase in the active areas of the brain. The PET detects the area of the brain that is most active during the task. The disadvantages of PET are the radiation exposure and the relatively slow scanning time that limits the number of areas of the brain that can be studied in any one person at any one time. Although less precise than PET, the single photon emission computed tomography (SPECT) utilizes a radioisotope to measure cerebral blood flow. It can be used to identify areas of hypoperfusion in the brain, such as might be seen in areas of neuronal degeneration in dementia. PET and SPECT can also be used to measure receptor or enzyme binding, although at this point, the technology is not used routinely in clinical practice.

The fMRI has the advantages of coupling structural scanning with images of brain activation, not requiring radiation exposure, and being completely noninvasive. Indirect measures of blood flow and metabolism are made by measuring the ratio of oxyhemoglobin (oxygenated form of hemoglobin) to deoxyhemoglobin (hemoglobin that has donated its oxygen). This technique is called blood oxygen level–dependent contrast. FMRI is the most widely used neuroimaging technique for studying cognitive dysfunction. Examples of how fMRIs have helped us understand more about cognitive dysfunction comes from studies of individuals with schizophrenia and depression. During working memory tasks, individu-

als with schizophrenia sometimes show hypoactivation of the prefrontal cortex and other times show hyperactivation. The hypoactivation illuminates the difficulties that they have with staying on task, and the hyperactivation illuminates the reduced efficiency of their prefrontal cortex (Weinberger et al., 2001). In depression, hyperactivation of certain prefrontal networks at rest is congruent with rumination and excessive self-focus (Sheline, Price, Yan, & Mintun, 2010). Finally, innovative fMRI approaches include testing the effects of drug administration while persons are engaged in complex cognitive tasks (Pearlson & Calhoun, 2007). These types of findings would not have been possible using structural neuroimaging methods.

Electroencephalography

In electroencephalography (EEG) the pattern of the brain activity on the surface of the brain is visible, but the origin of the activity from within the brain's regions is not.

Electroencephalography (EEG) is the measurement of electrical currents at the scalp that reflect events within the brain. Groups of brain cells that fire synchronously generate electrical potentials that can be measured on the surface of the brain, however, the origin of activity from specific brain regions cannot. Magnetoencephalography (MEG) is a technique that measures magnetic currents at the scalp to detect neural activity deep within the brain. It is noninvasive but is limited to use in research.

Conclusions

Neurobiologic considerations in psychiatric care include clinical expressions of psychiatric illness, genetic contributions, and environmental risk factors. As we gain further knowledge about gene–environment interactions and the reversible epigenetic changes in gene expression, we will have greater ability to identify targets for prevention and intervention. Given what we already know about the deleterious effects of early life stress on the HPA regulation, the brain and metabolic consequences of chronic stress, and the neuroadaptations that occur with drug abuse, psychiatric nurses are positioned to make advances in primary prevention, screening, and treatment.

National reports and initiatives, such as the President's Freedom Commission (2003) and the Institute of Medicine's (2005) report, *Improving the Quality of Health Care for Mental and Substance-Use Conditions*, and the Department of Health and Human Services' Substance Abuse and Mental Health Services Administration's (SAMHSA, 2005) Action Steps for Transforming Mental Health Care, advocate transforming the mental health system to be more evidence-based and consumer driven. This will require nurses to keep up with the changes in our knowledge base regarding the causes and treatments of mental illness and to help translate these findings to patients/clients and their families so that they can make informed decisions regarding their care. Helping clients, families, and the community at large understand the neurobiological considerations will help decrease the stigma and improve the care of individuals with mental illness.

Summary

This chapter has provided a basic knowledge of the brain's structures and their functions, the neurotransmitters and their pathways, and the mechanisms for the development of mental illnesses and disorders and their treatment. There was focused discussion of the structure and function of the nervous system, cellular mechanisms of communication, the role of neurotransmitters in mental illness, neurotransmission and neuroplasticity, the regulation of emotion and the limbic system, stress response (acute and chronic), and genetic factors. Conditions specifically discussed included mood disorders, anxiety, schizophrenia, and dementias. The role of various tests were presented: neuroimaging (CT, MRI, MRS, DTI), functional imaging (fMRI, PET), and electroencephalography (EEGs). The relationship between neurobiology and psychopharmacological treatment was highlighted.

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