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Basic and Applied Science: The Neuroscience of Mental Disorders

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ANATOMY AND PHYSIOLOGY THROUGH THE LIFE SPAN

In this chapter, we will examine the anatomy (structure) and physiology (function) of the nervous system, as well as major theories regarding the disruption of normal physiological functioning (pathophysiology) in selected mental disorders.

Physical Development

At birth, infants normally display characteristic primitive reflexes that include grasping, rooting, sucking, startle (moro), and Babinski reflex (toes spread when sole of foot is touched). The Babinski reflex disappears by about 1 year; the others, by about 4 months. By around 2 weeks of age, an infant prefers the mother's voice and has the ability to discriminate colors, smells, and tastes. Although development proceeds a bit differently for each individual, on average, other physical milestones include: balancing the head (4 months); sitting unsupported (6 months); pulling to feet (10 months); walking and grasping small objects (12–16 months); running (2 years); jumping, dancing, and drawing or copying simple objects (3 years); skipping (age 5); and riding a bike (6 years). The average age of puberty for girls is from 10 to 14 years, with menarche around 11 years; puberty for boys is from 10½ to 17½ years. At puberty, most individuals have a

growth spurt and develop secondary sex characteristics. With aging, we expect to see a decline in most physical systems (Table 6–1). In certain neurodegenerative disorders, such as dementia, the primitive reflexes may return.

Table 6–1. Examples of Changes in Physical Systems With Aging

Physical Systems	Changes with Aging
Neurological	• Decreases in neurons and some neurotransmitters • Brain becomes smaller and lighter • Vision and hearing loss • Continued ability to form new synapses
Endocrine	• Changes in production of most hormones, change in function may not occur
Respiratory	• Decline in respiratory muscle strength and control of breathing
Cardiovascular	• Heart and blood vessels stiffen • Cardiac output declines • Decreased ability of heart and vessels to stress
Gastrointestinal	• Liver, gallbladder, and pancreas continue to function well in the elderly • Decreased hepatic blood flow may decrease drug clearance
Genitourinary	• Decreased size of kidneys • Decreased renal blood flow • Creatinine clearance declines • Erectile dysfunction in approximately 67% by age 70 (Stahl, 2008)
Musculoskeletal	• Decline in muscle mass with increasing weakness • Bone loss
Integumentary	• Increased dryness • Increased thinning and decreased elasticity • Wrinkles, dryness, and age spots from excessive sunlight
Hematologic	• Decreased ability of bone marrow to produce rapid increases in red blood cells with blood loss.

Brain Development

At birth, infants weigh an average of only 7 pounds, yet their head size is approximately one-third the size of their entire body. Even though the brain is relatively large compared to the body, it has not finished developing. With the help of glial cells and growth factors, neurons

continue to migrate to their terminal sites within the frontal lobes, making connections with other neurons and laying down the structures that will guide executive functioning and self-regulation. Not until the late teens or early twenties is the development of the brain (and personality) complete. Throughout our lives, synapses are modified, solidifying memories or causing them to be forgotten. New neurons continue to be created in the area of the brain involved in consolidating long-term memories. Terms such as *neuroadaptation* and *neuroplasticity* describe the dynamic relationship between nature and nurture—between the brain and the environment.

NEUROANATOMY AND NEUROPHYSIOLOGY

The objectives of learning basic neuroanatomy and neurophysiology include gaining an ability to identify basic structures and functions within the nervous system, identifying neurotransmitter systems that are involved in psychiatric symptoms and disorders, and understanding the rationale for selected psychopharmacological interventions.

Organization of the Nervous System

The brain, brain stem, and spinal cord are the major structures of the central nervous system (CNS). The remainder of the nervous system is called the peripheral nervous system (PNS). The PNS is divided into the somatic branch that is involved in voluntary motor movement, and the autonomic branch (ANS) that controls the internal organs, blood vessels, and glands. The ANS is further divided into the sympathetic and parasympathetic branches. The activation of the sympathetic branch results in increased heart rate, respiration, blood pressure, and energy mobilization, and decreased digestive and reproductive functions. The parasympathetic branch of the nervous system serves more homeostatic functions by maintaining heart rate, respiratory, metabolic, and digestive functions under normal conditions.

The Brain

The brain weighs approximately 3 pounds, has several billion neurons, and has tens of billions of neuronal interconnections. The brain can be divided into three basic components: the cerebrum, the cerebellum, and the brain stem. The cerebrum is the outer- and upper-most part of the brain. Four major lobes are represented bilaterally, connected by a band of axons called the *corpus callosum*. In the majority of people, even those with left-hand dominance, verbal language functions are primarily represented in the left hemisphere, and nonverbal functions are primarily represented in the right hemisphere. Ascending and descending pathways carry information between the brain and spinal cord. The descending pathways traveling from the cortex to the spinal cord (corticospinal) cross to the opposite side in the brain stem. Thus an injury to the left frontal area of the brain may affect motor functioning on the right side of the body. By knowing the basic functions of the major lobes and structures, we can understand many of the behaviors and symptoms of psychiatric disorders. Descriptive terms referring to problems with higher level cognitive functioning are listed in Box 6–1.

Functions of the *frontal lobes* include motor control, executive functioning, working memory, and personality. Broca's area is the part of the motor cortex involved in the production of speech. Damage to this area can result in difficulty speaking and is referred to as *Broca's* (or nonfluent) *aphasia.* The foremost parts of the frontal cortex ("prefrontal cortex") are responsible for three major functions: 1) executive functioning, 2) working memory, and 3) personality. *Executive functioning* refers to decision-making, planning, organization, and impulse control. *Working memory* refers to an attentional system that can hold and manipulate information until it is transferred into long-term storage. Many of the psychiatric disorders (e.g., attention deficit-hyperactivity disorder, depression, schizophrenia) are characterized by deficits in executive and working memory functioning. The *personality* develops over the early years as a function of the interplay between the brain and the environment. By late adolescence or early adulthood, the personality stabilizes and changes very little over the remaining life span. Because of the stability of personality, when individuals do exhibit noticeable changes (e.g., becoming more outgoing, uninhibited, impulsive, socially withdrawn, apathetic), we should be concerned about frontal lobe functioning and refer for further evaluation.

The *temporal lobes* are especially important for hearing, interpreting language, learning and memory, and emotional responses. *Receptive aphasia* (inability to interpret spoken language) may result from damage to *Wernicke's area,* the functional part of the temporal cortex involved in the interpretation of language. Auditory hallucinations involve the temporal cortex, along with other structures of the brain. Located deep within the temporal cortices are important structures concerned with learning and memory. The *hippocampus* is responsible for consolidating long-term explicit memories for facts and events. *Amnesia,* defined as a severe loss of memory or learning, is reflective of injury to the hippocampus. Chronically elevated levels of cortisol, as seen in many individuals with depressive and anxiety disorders, appears to damage the hippocampus, and may be responsible for complaints related to learning and memory. Fortunately, the hippocampus is an area of the brain capable of generating new neurons, so recovery may be possible. The *amygdala* is a small structure located within the anterior medial portion of each temporal lobe that is important for detecting danger, recognizing emotions—especially negative ones—and recalling the emotional aspects of life events.

Box 6–1. Disturbances of Higher Level Cognitive Functioning

Aphasia: Disruption of language function
Apraxia: Disturbance in the organization of voluntary action (e.g., putting on one's clothes)
Agnosia: Disorganization of perception and recognition
Amnesia: Dysfunction of memory processes
Dementia: Deterioration in intellectual and cognitive functions

Functions of the *parietal lobes* include the somatosensory modalities of light touch, pressure, pain, temperature, vibration, and proprioception (position sense). The posterior portion of the parietal cortex helps us perceive and interpret spatial relationships, form an accurate body image, and learn tasks involving coordination of the body in space. When these areas become damaged, individuals may develop sensory *agnosias,* defined as the impaired ability to interpret sensory information (e.g., identifying a key in one's pocket by touch). Other examples of parietal dysfunction include graphomotor problems (e.g., drawing a clock or copying a figure) and spatial neglect (e.g., following a cerebrovascular accident). The *occipital lobes* are primarily responsible

for vision. A visual agnosia is the inability to recognize objects by using vision. Visual hallucinations involve the visual cortex along with other brain structures.

Deep within the cerebrum are other important structures. The *basal ganglia* are very important nuclei for initiation of voluntary movement. The basal ganglia are outside of the descending corticospinal ("pyramidal") motor tracts and are thus considered *extrapyramidal.* When we talk about *extrapyramidal symptoms* (EPS) involving unusual movements such as *bradykinesia* (slow movement) or *hyperkinesias* (fast movement such as ticks or tremors), we are referring to symptoms that reflect dysfunction of the basal ganglia. Parkinson's disease is caused by destruction of dopaminergic neurons that project into the basal ganglia, resulting in impaired motor functioning. "Parkinsonism" is due to blockade of the same dopaminergic neurons by antipsychotics.

The *thalamus* is a relay station between the spinal cord and cortex. It transmits incoming sensory information to the relevant cortical areas. Similarly, it transmits descending motor information from the cortex to other areas of the brain and spinal cord. Together with the reticular activating system (RAS) in the brain stem, the thalamus helps modulate arousal levels. The *hypothalamus* serves as a master regulatory center in the brain, regulating food and fluid intake, temperature, and the pituitary gland via the HPA axis.

The functions of the *cerebellum* include movement, balance, and posture. The cerebellum functions to maintain equilibrium and work together with the motor cortex and basal ganglia to control movement. The cerebellum specializes in calculating the sequence of muscle contractions necessary to achieve goals in voluntary movement. When the cerebellum is dysfunctional, we may see uncoordinated and inaccurate movements such as a wide based gait (*ataxia*), difficulties touching the finger to nose, and difficulties maintaining balance (Romberg test).

The *brain stem* includes the midbrain, pons, and medulla. Neurotransmitter-producing cell bodies are clustered in the brainstem with projections that travel to diffuse areas of the brain. Brain stem cells that produce several of the neurotransmitters associated with psychiatric symptoms, disorders, and treatments include the *substantia nigra* (dopamine), *locus coeruleus* (norepinephrine), and *raphe nuclei* (serotonin). These neurotransmitter pathways are essential for modulating motor control, memory, mood, motivation, and metabolic state. The brain stem is also a major conduit for neuronal pathways that travel between the brain and periphery. The pons relays information between the cerebrum and the cerebellum. The medulla is the site of decussation (crossing over) of the descending pyramidal tracts. A brain injury below the level of decussation will have noticeable effects on the same side of the injury. A brain injury above the level of decussation will result in peripheral impairments on the opposite side of the body.

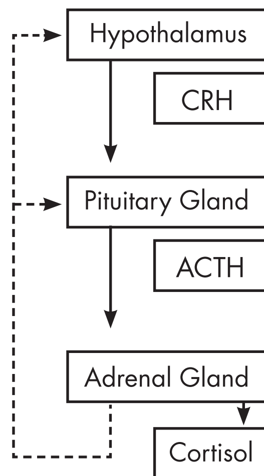
The *limbic system* is a group of brain structures important in the regulation of emotion and memory. The hippocampus and amygdala assure that we can recall the events of our lives along with their emotional valence. The olfactory system plays a very primitive role in triggering memories. In humans and primates, the frontal lobes participate in planning and decision-making parts. Disorders of emotion and memory involve the limbic structures and their connections.

Stress and the brain. The detection of threat by the amygdala triggers the hypothalamus to set off the stress response. The stress response involves two different major pathways: the ANS and

the HPA axis. Activation of the ANS leads to the release of peripheral epinephrine (also called adrenalin) from the adrenal medulla. Epinephrine increases the heart rate and blood pressure and prepares us to escape the perceived danger. This response, often called the *fight or flight* response, is frequently accompanied by *fright* or anxiety. Hans Selye, in his theory of the *general adaptation syndrome* (Selye, 1956), referred to this stage as the *alarm* reaction. If the stressor can be resolved, the alarm response subsides. If not resolved, the *resistance* stage is the body's continuing attempts to adapt. If adaptation fails, the eventual outcome is the stage of *exhaustion* and illness.

The second stress pathway is the HPA axis (Figure 6–1). The hypothalamus releases corticotrophin-releasing hormone (CRH), which triggers the pituitary gland to produce adrenocorticotropic hormone (ACTH). ACTH stimulates the adrenal glands to release cortisol. Cortisol works more slowly to increase the utilization of glucose and decrease inflammation—both important for dealing with acute stressors. If all goes well, active coping leads to a resolution of the stressor. The adaptive responses to stress have been referred to by McEwen (2008) as "allostasis." If the stressor is not resolved, wear and tear on the body increases (allostatic load) with continued cortisol secretion and risk for hyperglycemia, hyperinsulinemia, hypertension, increased cholesterol, and eventually arteriosclerosis. The hippocampus, particularly sensitive to cortisol, may experience atrophy with resultant problems with memory. In summary, although the stress response is protective and adaptive, chronic activation causes increasing wear and tear on the body and eventual pathophysiology.

Figure 6–1. HPA Axis



Neurons, Neurotransmitters, and Neurotransmitter Pathways

The brain tissue consists of two distinct types of cells: glia and neurons. The *glia* are the supporting structures of the brain, outnumbering neurons in a 10:1 ratio. In addition to providing support, they are important in guiding the migration of neurons during development and controlling the extracellular concentrations of potassium (K^+) and other ions. Some glia form the protective sheaths around the axons of neurons. This protective coating, *myelin,* is

what we refer to as white matter, whereas the uncoated neuronal cell bodies appear more gray and are referred to as gray matter.

Though less numerous, *neurons* are considered to be the more important "microprocessors" of the brain. They are responsible for the majority of the communication among structures of the brain and among the brain and other body parts. Though the exact number is unknown, there are estimated to be some 100 billion neurons in the brain. Each neuron receives input from tens of thousands of different neurons. The complexity is nearly unfathomable.

Neurons look and act differently than other cells. In common with most other cells in the body, they have nuclei that contain DNA. All cell bodies also contain liquid cytoplasm that surrounds the nuclei, and organelles that function to produce necessary proteins. Two regions of the neuron distinguish it from other common cells. The *dendrites,* having the appearance of branches, receive information from other cells. The *axons,* generally covered with myelin, send information to other cells. Myelin insulates the axons and allows the electrical signals (axon potentials) to travel quickly down the axon, regenerating at small breaks (nodes of Ranvier) in the myelin, until they reach the terminal.

Neurotransmitters. Once the electrical action potential reaches the neuron terminal, the release of neurotransmitter is triggered. The chemical neurotransmitter diffuses across the small space between the neurons (called the *synapse*) and activates the *receptors* of the post-synaptic cell. Each neurotransmitter has a specific mechanism for inactivation once it has activated the receptor and been released back into the synapse; it either diffuses out of the synapse, gets pumped back into the terminal for recycling, or gets broken down by enzymes such as monoamine oxidase (MAO).

Although more than 40 different neurotransmitters have been found to have CNS functions, the ones that we are most familiar with in psychiatric practice are the monoamines (Table 6–2). These include acetylcholine (ACh), dopamine (DA), norepinephrine (NE), epinephrine (E), and serotonin (5-HT). Even smaller amino acids that act as CNS neurotransmitters include glutamate, and gamma-aminobutyric acid (GABA). The monoamines and amino acid neurotransmitters can be produced right in the terminals where they will be used. Larger neuroactive peptides (large protein neurotransmitters such as beta-endorphin) are only produced in the cytoplasm of the nucleus and must be transported to the terminals.

Table 6–2. Monoamine and Amino Acid Neurotransmitters and Their Functions

Neurotransmitter	Partial List of Known Functions
Dopamine	Attention and executive functioning, motivated behaviors (reward- and pleasure-seeking), addictions, mood, movement, psychosis
Norepinephrine	Arousal, concentration, learning and memory, mood, stress response
Epinephrine (adrenaline)	Peripheral activation and arousal, fight or flight response

Continued

Table 6–2. Monoamine and Amino Acid Neurotransmitters and Their Functions (cont.)

Neurotransmitter	Partial List of Known Functions
Serotonin	Mood, anxiety, appetite, eating behavior, sleep
Acetylcholine	Arousal, cognition, memory, contraction of skeletal muscle
Glutamate	Excitation
GABA	Inhibition

PATHOPHYSIOLOGY OF MENTAL DISORDERS

Pathophysiology is concerned with alterations in function that accompany a particular syndrome or disease. The pathophysiology of each of the mental disorders is a function of alterations in brain function. The average age of onset of all of the adult psychiatric disorders is in early adulthood.

The Stress-Diathesis Theory of Mental Disorders

No mental disorder can be explained by a single gene. The heritability of mental disorders ranges from as low as 29% for depression to as high as 89% for bipolar disorder (Box 6–2). Rather, each mental disorder is probably associated with a number of vulnerability genes. Whether the genes will actually be expressed, resulting in symptoms of mental illness, may depend upon environmental factors. The stress-diathesis theory of mental disorders describes contributions of genetics (diathesis) and environment (stress). The term, diathesis, describes the tendency, vulnerability, or predisposition toward psychiatric symptoms based upon genetics. Stress refers to the environmental contributions. Early life stressors such as childhood trauma or neglect, significant loss, and possibly viruses or toxins, are important environmental contributors to mental disorders. Parental behaviors that might contribute to the risk for mental disorders in their offspring include starvation, poor nutrition, lack of vitamin D exposure, and substance abuse. For individuals who have a strong genetic disposition to develop a mental condition, it may not take much of a stressor to trigger the expression of the condition. Schizophrenia and bipolar disorder are the most heritable of the mental disorders. For individuals who are less vulnerable to mental disorders, it may take a larger number or greater intensity of stressors to trigger the onset. Some disorders such as posttraumatic stress disorder (PTSD) and phobias may be triggered by exposure to extreme stress in individuals with otherwise very little vulnerability.

Box 6–2. Heritability of Mental Disorders

Highest heritability
Schizophrenia (82%–84%) (Kendler, 2001)
Bipolar disorder (85%–89%) (McGuffin, Rijsdijk, Andrew, Sham, Katz, & Cardno, 2003)

Medium heritability
Alcoholism (52%–58%) (Kendler, 2001)

Lowest heritability
Anxiety disorders (37%–43%) (Kendler, 2001)
Major depression (29%–42%) (Kendler, Gatz, Gardner, & Pedersen, 2006)

Schizophrenia

The average age of onset for schizophrenia is 18–25 for males and 25–35 for females (American Psychological Association, 2000). Although rare, children and middle-aged adults also can develop the disorder. The date of onset is defined by the 6-month period of positive symptoms; however, the prodrome period leading up to the first acute episode may last days to years. Family members often can look back after the diagnosis of schizophrenia and identify a period of altered behavior leading up to the first major episode of psychosis. During this time, a teenager may withdraw from family or friends, use drugs, and exhibit changes in motivation and school performance. Subtle delays in language and motor skills may even have been present early in life. Following an acute episode of psychosis, recovery to previous levels of functioning may be incomplete, often characterized by the persistence of negative symptoms. The three major symptom categories of schizophrenia that reflect brain abnormalities are the positive symptoms (hallucinations, delusions, abnormal speech, abnormal behavior), negative symptoms (amotivation, apathy, anhedonia), and cognitive dysfunction (diminished executive functioning and working memory).

Neurodevelopmental abnormalities. Researchers have determined that very subtle early symptoms of schizophrenia may have been present from early childhood, including delayed language development and asymmetrical use of major muscles of the body. These early findings have led researchers to the hypothesis that schizophrenia is a neurodevelopmental condition. In other words, the brains of individuals who develop schizophrenia may not develop normally. It has been hypothesized that the early migration of neurons in brain development may be faulty, resulting in abnormal connections. Support for the neurodevelopmental theory comes from the observation that during the late teens, when most individuals develop full access to the frontal executive functions of the brain, the individual with schizophrenia starts to demonstrate disordered thinking.

Neurodegenerative abnormalities. In addition, the process of pruning away unnecessary connections in the brain may go awry, resulting in too much destruction of neurons and their connections. A process called "*excitotoxicity*" (Stahl, 2008) has been used to describe the potential self-destruction of neurons resulting from too much glutamate and excitatory neuronal activity. Support for a neurodegenerative mechanism in schizophrenia comes from monozygotic

twin studies showing that affected twins tend to have enlarged ventricles of the brain in comparison to their healthy twin siblings. Ventricular enlargement is due to atrophy of the brain tissues creating more space for fluid in the ventricles.

Neurotransmitter abnormalities. The pathophysiology of schizophrenia is also characterized by abnormal neurotransmission. Abnormally elevated levels of dopamine in the limbic system are thought to be responsible for positive symptoms. Because dopamine is essential for learning, memory, and motivation, the negative symptoms and cognitive impairment may reflect lower than normal levels of dopamine in the prefrontal cortex. Although dopamine is the neurotransmitter most associated with schizophrenia, researchers are learning that other neurotransmitters, such as glutamate, also may have important roles.

Mood Disorders

Disorders of mood can include depression or bipolar disorder, or the less acute but long-lasting dysthymic and cyclothymic variations. The distinction between unipolar depression and bipolar depression is important because the two disorders require different treatments. Bipolar depression is more likely to have a heritable (genetic) component than unipolar depression, and a person with bipolar disorder is more likely to have had previous symptoms, treatments, or hospitalizations. Depression can occur at any age, including the first and last years of life. Although the average age for diagnosing bipolar disorder is in the late 20s or early 30s, many of the symptoms, including impulsivity and difficulty controlling emotions, can be present as early as age 5 or 6. These early symptoms of bipolar disorder are often misdiagnosed as attention deficit-hyperactivity disorder (ADHD). Mood disorders can be triggered by upsetting life events, life transitions, physical transitions or illness, and by chronic stress.

Depression: Monoamine dysregulation. Monoamines are the neurotransmitters that include serotonin (5HT), norepinephrine (NE), and dopamine (D). The hypothesis that depression is caused by a reduction or deficit in one or more of the monoamines forms the basis for treating with the traditional antidepressants. The actual mechanism of depression is probably more complicated, involving the monoamine receptors and other cellular events, including the regulation of gene expression (Stahl, 2008).

Depression: Dysregulation of the HPA axis. A second hypothesis about the pathophysiology of depression involves the stress response systems, in particular the hypothalamus-pituitary-adrenal (HPA) axis. The HPA axis appears to be the main site where genetic and environmental influences converge to cause mood disorders. Early life stressors, such as the loss of a parent, trauma, or neglect, have been shown to produce lasting effects on the HPA axis, leading to chronic difficulty managing stress, and chronically elevated levels of cortisol. The support for this hypothesis of depression is that individuals with major depressive disorder often present with hypercortisolemia, resistance of cortisol to suppression by dexamethasone, blunted ACTH responses to corticotrophin-releasing hormone (CRH) challenge, and elevated CRH concentrations in the cerebrospinal fluid (CSF).

Bipolar disorder: Monoamine dysregulation. Bipolar manic episodes may involve the same neurotransmitter systems as depression, with problems related to over-activity rather than under-activity. Elevated levels of 5HT, NE, and D in areas of the brain regulating mood and behavior could explain symptoms such as irritable or expansive mood, pressured speech, flight of ideas,

decreased sleep, and increased goal-directed activity. Sensitivity and kindling are two terms that have been used to describe neuronal activity in bipolar disorder. Early in the course of the illness, mood episodes may be triggered by significant stressors. Over time, the brain appears to become sensitized to stress and much less stress is necessary to trigger an episode. The neurons respond to slight provocations like kindling wood for fire: a small puff of wind and the kindling catches on fire immediately.

Anxiety

Anxiety can be a normal emotion in threatening circumstances. It is the emotional component of the "fight or flight" stress response and has important survival functions. Anxiety can also be part of a syndrome or symptom complex associated with certain medical or substance-related conditions. Examples include hyperthyroidism, ADHD, and alcohol or benzodiazepine withdrawal. Finally, anxiety can be the primary component of a disorder. The anxiety disorders are characterized by fear and worry.

Anxiety is common at all ages. Children can develop all of the anxiety disorders experienced by adults, in addition to separation anxiety disorder. Separation anxiety is a normal stage of development around 6–18 months. However, separation anxiety becomes a disorder when school-aged children continue to express fear of separation along with significant functional impairment. Although anxiety has a heritable component, anxiety disorders such as PTSD and phobias occur following a threatening event.

Dysfunctional brain circuits related to threat perception. The neurobiology of fear is thought to involve brain circuits that are regulated by the amygdala, the small brain structure that is responsible for detecting threat and initiating the stress response. Worry may involve a different brain circuit that passes through the basal ganglia. The connection with the basal ganglia is especially important in obsessive-compulsive disorder (OCD), where we see overlap with other disorders that are linked to basal ganglia dysfunction, such as ADHD and tics.

Chronic stress response. Anxiety disorders and depression often share symptoms that are associated with a chronic stress response. Symptoms associated with chronic stress include tension headaches, migraine headaches, and musculoskeletal pain. In addition, a chronic response to stress via the HPA axis (Figure 6–1), with increased circulating levels of cortisol, has been linked to increased abdominal fat; impaired immune function; disrupted glucose metabolism; cardiovascular symptoms (e.g., hypertension); gastric ulcers; and hippocampal atrophy with learning and memory impairments.

Neurotransmitter dysregulation. We know that the brain's GABA receptors can be modulated by depressants such as alcohol and benzodiazepines. When people drink alcohol or take benzodiazepines, anxiety levels tend to subside. During withdrawal from those same substances, anxiety increases. These findings support the hypothesis that the neurotransmitter GABA and its receptors are important in the symptoms of anxiety. Too little GABA is associated with symptoms of anxiety. On the other hand, too much arousal from NE or glutamate may also lead to symptoms of anxiety.

Obesity and Eating Disorders

Obesity is associated with many health risks, including type 2 diabetes, heart disease, stroke, hypertension, osteoarthritis, sleep apnea, and some forms of cancer. Poor diet and sedentary lifestyle contribute to obesity; however, the chief contributor is heredity. The heritability of obesity is equivalent to that of height (Bear, Connors, & Paradiso, 2006), and as with all of the mental disorders, more than one gene is involved. Obesity can result from a variety of disorders that cause hormonal imbalance, including hypothyroidism, hypercortisolism, primary hyperinsulinism, pseudohypoparathyroidism, and acquired hypothalamic problems (e.g., tumors, infections, traumatic syndromes).

Recently, concern has been voiced regarding the risk of metabolic syndrome in individuals who are taking atypical antipsychotics. *Metabolic syndrome* includes the following symptoms: abdominal obesity, dyslipidemia, raised blood pressure, insulin resistance with or without glucose intolerance, proinflammatory state, and prothrombotic state. Individuals with metabolic syndrome are at risk for premature coronary heart disease.

Because many of the psychotropic medications can cause weight gain and increase the risk for metabolic syndrome, it is especially important that we monitor weight and body mass index (BMI) before and during treatment. BMI can be calculated based on weight and height, and BMI charts are readily available for both adults and children on websites such as the Centers for Disease Control and Prevention (http://www.cdc.gov/nccdphp/dnpa/healthyweight/assessing/bmi/index.htm) or the National Heart Lung and Blood Institute (http://www.nhlbisupport.com/bmi/). The normal range of BMI for adults is between 18.5 and 24.9, with 25 to 29.9 indicating overweight and anything over 30 indicating obesity.

Eating disorders. Anorexia and bulimia are eating disorders found primarily in highly developed cultures such as in the United States, especially those with a focus on youth and beauty. They are serious conditions that can be fatal if untreated. Both involve cognitive distortions around body shape and weight. Anorexia is characterized by refusal to maintain body weight at or above 85% of the expected based on age and height. Multiple physiological factors are involved in the complex regulation of eating. The self-induced state of starvation seen in anorexia has serious physical consequences including cardiac arrhythmias, bradycardia or tachycardia, hypotension, hypothermia, skin dryness with possible lanugo (a soft, fine, downy hair on the arms and other body parts that is normal in infancy), edema, and amenorrhea. Basically, all organ systems are affected by starvation. Hospitalization is indicated for patients who are 20% or more below the expected weight for their height.

Bulimia is characterized by recurrent episodes of binge eating followed by inappropriate compensatory mechanisms. Vomiting or laxative abuse can lead to metabolic disturbances and electrolyte abnormalities (e.g., hypokalemia, hypochloremic alkalosis, hypomagnesemia). Recurrent self-induced vomiting can result in the loss of dental enamel, scars on the hand, and esophageal tears.

Addictions

Genetic factors and environmentally induced alterations in brain neurochemistry appear to influence vulnerability for addiction. Addictions are a chronic, relapsing disease of the brain characterized by compulsive drug-seeking and use (Volkow, 2008). All drugs of abuse are thought to increase brain dopamine in the pathways that drive motivation and reward. Chronic use of alcohol or other drugs may produce alterations in brain neurochemistry that help to maintain addictive behaviors. Higher rates of substance abuse are found in impulsive groups: violent offenders, conduct disorder, intermittent explosive disorder. Stress increases alcohol and drug use, and is associated with higher rates of relapse. Substance use disorders are frequently comorbid with other mental disorders. For further information about the effects of specific substances on brain neurophysiology, visit the website of the National Institute on Drug Abuse: http://www.nida.nih.gov.

Attention Deficit-Hyperactivity Disorder (ADHD)

Attention deficit-hyperactivity disorder (ADHD) is characterized by inattentiveness, impulsiveness, and hyperactivity. By definition, the symptoms must be present before age 7, but the diagnosis can be made at any age. Possible risk factors for the development of ADHD include genetics, perinatal complications, neurologic illness, diet, allergy, and environmental toxins. The neurobiology of ADHD is complex. ADHD is highly comorbid with anxiety, depression, and other mental disorders. The overlap of ADHD with obsessive compulsive behaviors and motor tics suggests that the basal ganglia and the motor pathway that produces dopamine and travels to the basal ganglia (the nigrostriatal pathway) are involved. In addition, executive functioning problems (impulsivity, impaired attentional and organizational skills) suggest frontal lobe abnormalities. The neurotransmitters that have been associated with the attentional and hyperactivity deficits are dopamine and norepinephrine, and with impulsivity, serotonin.

Dementia

There are many different types of dementia, including Alzheimer's, Lewy body, frontotemporal, and HIV. The most common cause of dementia is Alzheimer's disease (AD). Nearly 10% of individuals over the age of 65 and 25% to 40% of individuals over the age of 85 have AD (Breitner et al., 1999). Early changes in Alzheimer's disease and other dementias appear to be related to a decrease in the brain's levels of acetylcholine (ACh), a neurotransmitter essential to learning and memory. Support for this assumption comes from the observation that boosting cholinergic functioning with cholinesterase inhibitors (therefore reducing the metabolism and increasing the availability) enhances memory function in early dementia. As Alzheimer's dementia progresses, deposits of a protein called amyloid, and bundles of tangled proteins called neurofibrillary tangles, begin to interfere with the functioning of neuronal cells. The process of excitotoxicity related to glutamate overactivity is also thought to be responsible for some of the neurodegeneration and atrophy of the brain seen on MRI scans.

There are many differences between the pathophysiologies of the different dementias. *Lewy body dementia* is more common in individuals with Parkinson's disease and is characterized by the deposition of Lewy bodies (a protein) in the neurons. Individuals with Lewy body dementia

may have visual hallucinations, a characteristic that distinguishes them from other dementias. *Frontotemporal (Pick's)* dementia is characterized by atrophy in the frontal and temporal brain regions due to neuronal loss, gliosis, and Pick's bodies (masses of cytoskeletal elements). A distinguishing characteristic of *vascular dementia* is that cognitive functioning may decline in a stair-step (rather than progressive) fashion following cerebrovascular accidents.

In HIV-infected individuals, a dementia can result from the direct effects of HIV infection in the brain, opportunistic infections, or the toxic effects of drug treatments. The HIV virus may gain entrance to the CNS by infecting the macrophages and monocytes that cross the blood–brain barrier. Symptoms of the resulting AIDS dementia complex can be confused with clinical depression due to the presentation of apathy and cognitive and motor problems.

Delirium

Delirium is a serious medical condition that can be caused by any number of disturbances (see the "I Watch Death" mnemonic in Box 6–3). Unlike dementia, which is generally a slowly progressing condition, delirium can come on rapidly and is characterized by a clouding of consciousness with disorientation. Whereas someone with dementia may remain relatively oriented until the later stages of the illness, individuals with delirium may shift between periods of orientation and disorientation.

Box 6–3. I WATCH DEATH: A Mnemonic

- **I**nfection
- **W**ithdrawal
- **A**cute metabolic disturbance
- **T**rauma
- **C**NS pathology
- **H**ypoxia
- **D**eficiencies
- **E**ndocrinopathies
- **A**cute vascular
- **T**oxins
- **H**eavy metals

Sundowning is the term used for the disorientation that individuals with dementia may experience when familiar environmental cues diminish with nighttime. If delirium is suspected, it is important to alert the medical team so a complete physical assessment can be completed. Often, in older persons, an infection such as pneumonia or a urinary tract infection is found to be the culprit.

Comorbidities

Mental disorders are frequently comorbid with each other. Examples include depression and anxiety (Stahl, 2008); eating disorders and depression (Stahl, 2008); and dementia and depression, anxiety, or psychosis (Kverno, Rabins, Blass, Hicks, & Black, 2008). According to the National Institute of Drug Abuse (NIDA, 2007), patients with mood or anxiety disorders are about twice as likely to also suffer from a drug disorder. The highest comorbidity appears to be with mania, with nearly 40% of affected individuals having a lifetime prevalence of a drug disorder (NIDA, 2007). Pediatric diagnoses can be atypical, constantly changing, and unusually comorbid with other psychiatric disorders. ADHD, for example, is frequently comorbid with anxiety, depression, conduct disorder, oppositional behavior, substance abuse, and tics (Stahl, 2008).

Human Sexuality, Sexual Dysfunction, and Risks

The three phases of the sexual response cycle—libido, arousal, and orgasm—all have distinct and relatively non-overlapping neurotransmitter functions (Stahl, 2008). Each stage of the cycle can be affected by mental disorders or their treatments. Depression and anxiety are commonly associated with sexual dysfunction. Manic episodes may result in increased libido and sexual behavior. Of the neurotransmitter systems that we have discussed in relation to the mental disorders, dopamine and the brain reward pathways are thought to play a role in increasing libido or sexual desire. Serotonin has a negative influence, and norepinephrine a positive influence, on sexual arousal and orgasm. When we consider that most of the psychotropic drugs affect these three neurotransmitter systems, it is not surprising that sexual dysfunction is often an unwanted side effect of treatment.

Sexually transmitted diseases include syphilis, gonorrhea, chlamydia, trichomoniasis, human papillomavirus (HPV), herpes simplex virus, and HIV. HPV causes genital warts, and is associated with an increased risk for cervical cancer. A new HPV vaccine is available to girls ages 11 and older. Syphilis is caused by a spirochetal bacterium that, if not diagnosed or treated, can cause dementia via the slow, progressive infection of the brain.

Vulnerable populations at risk for HIV are individuals who have unprotected sex with multiple partners, IV drug users, gay men, hemophiliacs, and children born to HIV+ women. The routes of transmission of HIV are the blood and body fluids, usually through sexual contact, contaminated IV needles, or transfusions. Once inside the body, the HIV virus targets the CD4 receptor on the T4 lymphocytes. The virus injects its RNA into the infected lymphocyte and becomes part of cell division, eventually disabling the patient's T4 lymphocytes and impairing immune functioning. About 6 months after exposure, the individual can test positive for HIV. Therefore, those at risk need to be tested about every 6 months. The Centers for Disease Control and Prevention (CDC) recommends a diagnosis of AIDS when the T4 concentration falls to 20% of normal. The diagnosis of AIDS is also made following an opportunistic infection, sometimes up to 10 to 17 years after exposure to HIV. New antiretroviral drugs have lengthened the time from exposure to the development of AIDS and AIDS dementia.

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