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61

Disorders of Mood and Anxiety

Depression, bipolar disorder, and anxiety disorders have been well documented in medical writings since ancient times. In the fifth century BC, Hippocrates taught that moods depended on the balance of four humors—blood, phlegm, yellow bile, and black bile. An excess of black bile (*melancholia* is the ancient Greek term for black bile) was believed to cause a state dominated by fear and despondency. Robert Burton's *Anatomy of Melancholy* (1621) was not only an important medical text but also viewed literature and the arts through the lens of melancholia. Such texts describe symptoms that remain familiar today; they also recognized that symptoms of depression and of anxiety often occur together.

In this chapter, we discuss mood and anxiety disorders together, not only because they frequently co-occur but also because of overlapping genetic and environmental risk factors and some shared neural structures, including regions of the amygdala, hippocampus, prefrontal cortex, and insular cortex.

Mood Disorders Can Be Divided Into Two General Classes: Unipolar Depression and Bipolar Disorder

There are no objective medical tests for mood and anxiety disorders. Thus, diagnosis depends on observation of symptoms, behavior, cognition, functional

impairments, and natural history (including age of onset, course, and outcome). Patterns of familial transmission and response to treatment can also inform diagnostic classification. Based on such factors, it is possible to distinguish between two major groupings of mood disorders: unipolar depression and bipolar disorder. Unipolar depression, when severe and pervasive, is classified as major depression or major depressive disorder. Major depression is diagnosed when people suffer from depressive episodes alone. Bipolar disorder is diagnosed when episodes of mania also occur.

The lifetime risk of major depressive disorder in the United States is approximately 19%. Within any 1-year period, 8.3% of the population suffers major depression. The prevalence of depression differs in different countries and cultures; however, in the absence of objective medical tests, such epidemiologic data are subject to diagnostic and reporting biases, and thus, it is difficult to draw comparative conclusions. The World Health Organization reports that depression is a leading cause of disability worldwide, and other studies find it to be a leading cause of economic loss from noncommunicable disease. These dire social and economic consequences occur because depression is common, often begins early in life, and interferes with cognition, energy, and motivation, which are all necessary to learn in school and to work effectively.

Bipolar disorder is less common than unipolar depression, with a prevalence of approximately 1% worldwide. Its symptoms are relatively constant across countries and cultures. The incidence of bipolar disorder is equivalent in males and females.

Major Depressive Disorder Differs Significantly From Normal Sadness

Several factors distinguish major depression from transient periods of sadness that may occur in everyday life and from the grief that often follows a personal loss. These include the life context in which symptoms occur, their duration and pervasiveness, and their association with physiological, behavioral, and cognitive symptoms (Table 61–1). In healthy people, mood alternates between low and high, with timing and intensity phased appropriately with interpersonal interactions and life events. Mood states that are contextually inappropriate, extreme in amplitude, rigid, or prolonged are suggestive of either depression or mania, depending on their valence.

Depressive episodes, whether associated with unipolar or bipolar illness, are characterized by negative mood states such as sadness, anxiety, loss of interests, or irritability lasting for most of the day, day in and day out, and unrelieved by events that were previously enjoyable. This loss of interest is well expressed

Table 61–1 Symptoms of Mood Disorders

Five or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad, empty, hopeless) or observations made by others (eg, appears tearful).
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3. Significant weight loss when not dieting, or weight gain (eg, a change of >5% of body weight in a month), or decrease or increase in appetite nearly every day.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Source: Adapted from the American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American Psychiatric Association.

by Hamlet's complaint, "How weary, stale, flat, and unprofitable seem to me all the uses of this world!" When depression is severe, individuals may suffer intense mental anguish and a pervasive inability to experience pleasure, a condition known as anhedonia.

Physiologic symptoms of depression include sleep disturbance, most often insomnia with early morning awakening, but occasionally excessive sleeping; loss of appetite and weight loss but occasionally excessive eating; decreased interest in sexual activity; and decreased energy. Some severely affected individuals exhibit slowed motor movements, described as psychomotor retardation, whereas others may be agitated, exhibiting such symptoms as pacing. Cognitive symptoms are evident in both the content of thoughts (hopelessness, thoughts of worthlessness and guilt, suicidal thoughts and urges) and in cognitive processes (difficulty concentrating, slow thinking, and poor memory).

In the most severe cases of depression, psychotic symptoms may occur, including delusions (unshakable false beliefs that cannot be explained by a person's culture) and hallucinations. When psychotic symptoms occur in depression, they typically reflect the person's thoughts of being undeserving, worthless, or bad. A severely depressed person might, for example, believe that he is emitting a potent odor because he is rotting from the inside.

The most severe outcome of depression is suicide, which represents a significant cause of death worldwide; the World Health Organization estimates that there are 800,000 deaths by suicide annually. More than 90% of suicides are associated with mental illness, with depression being the leading risk factor, especially when accompanied by substance use disorders.

Major Depressive Disorder Often Begins Early in Life

Major depressive disorder often begins early in life, but first episodes do occur across the life span. Those who have had a first episode in childhood or adolescence often have a family history of the disorder and have a high likelihood of recurrence. Once a second episode has occurred, a pattern of repeated relapse and remission often sets in. Some people do not recover completely from acute episodes and have chronic, albeit milder, depression, which can be punctuated by acute exacerbations. Chronic depression, even when symptoms are less severe than those of an acute episode, can prove extremely disabling because of long-term erosion of a person's ability to function in life roles. Major depressive disorder in childhood occurs equally in males and females. After puberty, however, it occurs more commonly in females; the ratio of females to males is approximately 2:1 across countries and cultures.

A Diagnosis of Bipolar Disorder Requires an Episode of Mania

Bipolar disorder is named for its chief symptom, swings of mood between mania and depression; indeed, the influential 19th-century psychiatrist Emil Kraepelin called this condition the manic-depressive insanity. By convention, a diagnosis of bipolar disorder requires at least one episode of mania. Mania is typically associated with recurrent episodes of depression, whereas mania without depression is distinctly uncommon.

Manic episodes are typically characterized by elevated mood, although some individuals are predominantly irritable. During manic episodes, individuals have markedly increased energy, a decreased need for sleep, and occasionally a decreased desire for food (Table 61–2). People with mania are typically impulsive and engage excessively in reward-directed

Table 61–2 Symptoms of a Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week (or any duration if hospitalization is necessary).

B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted and have been present to a significant degree:
   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep (eg, feels rested after only 3 hours of sleep).
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (ie, attention too easily drawn to unimportant or irrelevant external stimuli).
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (ie, purposeless non–goal-directed activity).
   7. Excessive involvement in pleasurable activities that have a high potential for painful consequences (eg, engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

Source: Adapted from the American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American Psychiatric Association.

behaviors, often with poor judgment characterized by extreme optimism. For example, a person may go on spending sprees well beyond his or her means or on uncharacteristic binges of drug and alcohol use or sexual behavior. Self-esteem is typically inflated, often to delusional levels. For example, an individual might falsely believe himself to have extensive influence on events or to be a significant religious figure. In antiquity, mania was described as "a state of raving madness with exalted mood." However, such elevated mood may be brittle, with sudden intrusions of anger, irritability, and aggression.

Mania, like depression, affects cognitive processes, often impairing attention and verbal memory. During a manic episode, a person's speech is often rapid, profuse, and difficult to interrupt. The person may jump quickly from idea to idea, making comprehension of speech difficult. Psychotic symptoms commonly occur during manic episodes and are generally consistent with the person's mood. For example, people with mania may have delusions of possessing special powers or of being objects of adulation.

The depressive episodes that occur in bipolar disorder are symptomatically indistinguishable from those in unipolar depression, but are often more difficult to treat. For example, they are often less responsive to antidepressant medications. Longitudinal studies have found that the most common affective state of bipolar patients between severe acute episodes of mania or depression is not healthy mood (euthymia), as was often taught in older textbooks, but a state of chronic depression.

Historically, the concept of bipolar disorder described patients who experienced full manic episodes, which often included psychotic symptoms and necessitated hospitalization (Table 61–2). In recent decades, diagnostic classifications have added type 2 bipolar disorder in which mild manias (also called hypomanias) alternate with depressive episodes. The manic episodes of type 2 bipolar disorder are, by definition, not accompanied by psychosis or severe enough to require hospitalization. Whether this represents a variant of classic (type 1) bipolar disorder or some other pathophysiology is not yet known, although genetic dissection of mood disorders may offer some clarification in the near future.

Bipolar disorder generally begins in young adulthood, but the onset may occur earlier or as late as the fifth decade of life. Many manic episodes often lack an obvious precipitant; however, sleep deprivation can initiate a manic episode in some individuals with bipolar disorder. For such individuals, travel across time zones or shift work represents a risk. The rate of cycling among mania, depression, and periods of normal mood varies widely among bipolar patients. Individuals with short, rapid cycles tend to be less responsive to mood-stabilizing drugs.

Anxiety Disorders Represent Significant Dysregulation of Fear Circuitry

Anxiety disorders are the most common psychiatric disorders worldwide. In the United States, 28.5% of the population suffers from one or more anxiety disorders over the course of their lifetimes. Some anxiety disorders are mild, such as the simple phobias that involve rarely encountered stimuli; others, such as panic disorder or posttraumatic stress disorder, are often highly debilitating based on the severity of symptoms, interference with functioning, and chronicity.

Anxiety and fear are related emotional states; both are critical to surviving dangers that might be encountered throughout life. The major distinction is that fear is a response to threats that are present and clearly signify danger, whereas anxiety is a state of readiness for threats that are less specific either in proximity or timing. The neural circuits of fear and anxiety strongly overlap, as do their physiological, behavioral, cognitive, and affective aspects.

Fear is normally a transient adaptive response to danger that, like pain, serves as a survival mechanism. Like pain, fear is alerting and aversive and motivates more or less immediate behavioral responses. Thus, fear interrupts ongoing behaviors, supplanting them with such responses as avoidance or defensive aggression. To prepare the body to cope physiologically, fear circuitry activates the sympathetic nervous system and causes release of stress hormones. This "fight or flight" response facilitates blood flow to skeletal muscle, increases metabolic activity, and elevates pain thresholds. Like reward and other survival-relevant emotional responses, fear strongly facilitates the encoding and consolidation of both implicit and explicit memories that prepare an organism to respond rapidly and effectively to future predictive cues. (Fear circuitry is described in Chapter 42.)

Many cognitive and physiological components of anxiety are similar to fear, but typically exhibit lower intensity and a more protracted time course. Anxiety is adaptive when proportionate to the probability and likely severity of a threat, leading to appropriate levels of arousal, vigilance, and physiological preparedness. Given the dangerous, indeed potentially lethal, consequences of ignoring even ambiguous threat cues, failure to mount appropriate anxiety responses can prove

highly maladaptive. However, excessive contextually inappropriate and prolonged vigilance, tension, and physiological activation can be the basis of distressing and disabling anxiety disorders or anxiety symptoms that may accompany depression. Risk factors for anxiety disorders include a person's genetic background, developmental experience, and lessons learned not only from direct experience but also taught by families, peers, schools, and other institutions.

Cues that elicit anxiety may be environmental or interoceptive (ie, arising from within the body, such as abdominal discomfort or heart palpitations). Social cues and social situations can be a major source of anxiety. In humans, anxiety states can also be initiated by trains of thought that elicit memories or imagination of danger. Anxiety can also arise from stimuli that are processed unconsciously because of their brevity or ambiguity, and the resulting emotion might then be experienced as arising spontaneously. In contrast to fear, which is initiated and terminated by the presence or termination of clear stimuli denoting threat, anxiety has a more variable time course. Anxiety states may be prolonged if the potential for danger or harm is long-lasting or if there is no clear safety signal.

Anxiety disorders and the anxiety that may accompany major depression are associated with diverse symptoms. Affected individuals may develop excessive preoccupation with possible threats and attentional biases toward cues interpreted as threatening. Such cognitive states are often associated with persistent worry, tension, and vigilance. Common physiological symptoms include hyperarousal, as evidenced by a low threshold for being startled, difficulty sleeping, and sympathetic nervous system activation, including a rapid, pounding heartbeat. Individuals with anxiety may become exquisitely aware of their heartbeat or breathing, which can become a source of preoccupation and worry in their own right. Sympathetic nervous system activation may reach extreme levels of intensity during a panic attack, one of the most severe manifestations of anxiety.

In anxiety disorders, cognitive, physiological, and behavioral responses that would be adaptive in the face of a serious threat may be maladaptively activated by innocuous stimuli, may be inappropriately intense for the situation, and may have a protracted time course in which safety signals fail to terminate the symptoms. Affected individuals may avoid places, people, or experiences that, although objectively safe, have become associated with perceptions of threats or the experience of anxiety. When severe, such avoidance can impair the ability of affected individuals to function in different capacities or roles.

Because there are no biomarkers or objective medical tests for particular constellations of anxiety symptoms, current psychiatric classifications such as the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) classify anxiety disorders based on clinical histories, such as the nature, intensity, and time course of symptoms, the role of external cues in triggering episodes, and associated symptoms. The DSM-5 divides pathological anxiety syndromes into several distinct disorders: panic disorder, posttraumatic stress disorder, generalized anxiety disorder, social anxiety disorder (previously called social phobia), and simple phobias. For heuristic purposes, these disorders are discussed below, but current evidence from long-term clinical observation and from family, twin, and epidemiological studies does not support dividing anxiety symptoms into discrete nonoverlapping categories. Rather, the evidence suggests that pathological anxiety symptoms and symptoms of depression might be better conceptualized as a continuum or spectrum in which individuals experience varying symptoms that cross current DSM boundaries.

Consistent with the concept of a symptom spectrum, anxiety disorders and depression do not often occur together across generations in families as distinct DSM-5 categories; instead, diverse patterns of anxiety and depressive symptoms are typically observed among affected family members. Twin studies that compare concordance for traits in monozygotic and dizygotic twin pairs find significant shared genetic risk across multiple anxiety disorders and major depression. In addition, epidemiological studies find that individuals diagnosed with one categorical DSM-5 anxiety disorder, during, for example, teen years, have a high probability of developing new anxiety or depressive symptoms over the next decade that could result in the person being diagnosed with multiple disorders based on DSM-5 classifications. The high frequency at which putatively distinct DSM-5 anxiety disorders and depression co-occur and the results of family and twin studies suggest significant sharing of etiologic factors and pathogenic mechanisms among anxiety disorders and major depression. Nevertheless, individual disorders that are listed in DSM-5 are briefly described below.

Panic attacks are a severe manifestation of anxiety. They are characterized by discrete periods (that can last for many minutes) of intense foreboding, a sense of doom, fear of losing control over oneself, or fear of death. They are associated with prominent bodily symptoms such as heart palpitations, inability to catch one's breath, sweating, paresthesias, and dizziness (Table 61–3).

Table 61–3 Symptoms of a Panic Attack

A discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes.

1. Palpitations, pounding heart, or accelerated heart rate
2. Sweating
3. Trembling or shaking
4. Sensations of shortness of breath or smothering
5. Feeling of choking
6. Chest pain or discomfort
7. Nausea or abdominal distress
8. Feeling dizzy, unsteady, lightheaded, or faint
9. Chills or heat sensations
10. Paresthesias (numbness or tingling sensations)
11. Derealization (feelings or unreality) or depersonalization (being detached from oneself)
12. Fear of losing control or "going crazy"
13. Fear of dying

Source: Adapted from the American Psychiatric Association. 2013. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Washington, DC: American Psychiatric Association.

Panic attacks often give rise to anxiety about future episodes such that the contexts in which attacks have occurred can become phobic stimuli that trigger subsequent attacks (fear conditioning). As a result, some severely affected individuals restrict their activities to avoid situations or places in which panic attacks have occurred or from which they fear they might not be able to escape should they experience an attack. The most severely affected may develop generalized phobic avoidance, leading them to become housebound, a state described as agoraphobia. Current diagnostic classification systems such as the DSM-5 define panic disorder based on the number and frequency of attacks and whether or not a phobic trigger can be identified. Such detailed criteria lack a strong empirical basis, but it is certainly the case that individuals who have recurrent panic attacks along with other anxiety symptoms are not only highly distressed but may also be significantly disabled.

Posttraumatic stress disorder (PTSD) follows an experience of severe danger or injury. Under different names and descriptions, including shell shock, a term coined during World War I, PTSD has long been recognized as a result of combat. More recently, civilian traumas such as assault, rape, or automobile crashes have been recognized as potential causes of PTSD. The current approach to PTSD was formalized by the American Psychiatric Association based on the experience of Vietnam War veterans.

PTSD is initiated by a traumatic experience. Its cardinal symptoms include intrusive reexperiencing of the traumatic episode, typically initiated by cues such as sounds, images, or other reminders of the trauma. For example, a person who has been assaulted might respond potently to an unexpected touch from behind. Such episodes are often characterized by activation of the sympathetic nervous system and, when severe, may be characterized by "fight or flight" responses. The reexperiencing of a traumatic event may also occur in the form of nightmares. Other symptoms of PTSD include emotional numbness that may interfere with relationships and social interactions, insomnia, chronic hyperarousal including excessive vigilance, sympathetic nervous system activation, and an exaggerated startle response to an innocuous stimulus such as a touch or sound.

Generalized anxiety disorder (GAD) is diagnosed when a person suffers chronic worry and vigilance not warranted by circumstances. The worry is accompanied by physiological symptoms such as heightened sympathetic nervous system activation and motor tension. GAD commonly co-occurs with major depressive disorder.

Social anxiety disorder is characterized by a persistent fear of social situations, especially situations in which one is exposed to the scrutiny of others. The affected person has an intense fear of acting in a way that will prove humiliating. Stage fright is a form of social anxiety that is limited to circumstances of performance, such as public speaking. Social anxiety disorder can lead to avoidance of verbal classroom participation or communicating with others at work and can therefore prove disabling as well as distressing.

Simple phobias consist of intense and inappropriately excessive fear of specific stimuli, such as elevators, flying, heights, or spiders.

Both Genetic and Environmental Risk Factors Contribute to Mood and Anxiety Disorders

Bipolar disorder, major depression, and anxiety disorders all run in families. Twin studies that compare the rate of concordance of monozygotic and dizygotic twin pairs demonstrate significant heritabilities among these disorders, where heritability represents the percentage of the variation in a phenotype explained by genetic variation. Among mood and anxiety disorders, bipolar disorder has the highest heritability (70%–80%); major depression and anxiety disorders exhibit lower but still significant heritabilities (approximately 35%), with greater roles for developmental

and environmental risk factors. Although there is an important role for genes in the pathogenesis of mood and anxiety disorders, all of them exhibit non-Mendelian patterns of transmission across generations, including frequent co-occurrence of major depression and anxiety disorders. Such patterns reflect the complexity of genetic and nongenetic risk factors.

Molecular genetic studies aimed at discovering the precise DNA sequence variants (alleles) that predispose to mood and anxiety disorders have been initiated. Such studies are challenging because the risk architecture of these, and indeed all, common psychiatric disorders is highly polygenic, meaning that population risk appears to involve many thousands of common and rare alleles linked to or contained within many hundreds of genes. Unlike some neurologic disorders such as Huntington disease, there is no "depression gene" or "anxiety gene." Disease-associated alleles confer small additive effects on the risk of an illness. The risk for any given individual results from genetic loading (comprised of diverse combinations of disease-associated alleles) acting in concert with developmental and environmental factors. This polygenic architecture explains non-Mendelian patterns of transmission and the diverse combinations of depressive and anxiety symptoms observed within families and across populations.

The lack of objective diagnostic tests for mood and anxiety disorders means that any study cohort is likely to have some proportion of diagnostic misclassification. As a result, the search for common disease-associated variants by genome-wide association studies (GWAS) and rare disease-associated variants by DNA sequencing requires significant statistical power conferred by very large cohorts and by meta-analyses conducted across multiple cohorts. Early results of GWAS have been reported for major depression and bipolar disorder; in both cases, several significant genome-wide loci have been found to date, but not yet enough to identify molecular pathways of pathogenesis with any certainty. Whole-exome sequencing (ie, DNA sequencing of all genomic regions that encode proteins) and whole-genome sequencing are being conducted for bipolar disorder.

The highly polygenic risk architecture of mood and anxiety disorders means that there is no diagnostic value in testing for one or a few risk gene variants that might be associated with these disorders. Rather, polygenic risk scores (PRS), based on the sum of all genetic risk variants for a trait, are emerging as useful tools to stratify individuals in epidemiological and clinical studies by severity of genetic risk. A discrepant PRS within a clinical cohort, eg, showing low depression risk in a study of people with major depression, would suggest misclassification. It is important to emphasize that the polygenic nature of risk for mood and anxiety disorders and the significant contribution of environmental risk factors mean that, like any genetic test, the PRS provides only a probability.

As more is learned, the PRS can be combined with other measures to yield a more predictive risk score, just as modern cardiac risk models increasingly include genetic measures, smoking history, lipid levels, and blood pressure. For mood and anxiety disorders, one type of measure that shows early promise is identification of intrinsic patterns of neural connectivity derived from resting-state functional magnetic resonance imaging (fMRI; imaging conducted when subjects are not engaged in task performance). Differing patterns of connectivity could potentially distinguish among different forms of disorder.

Epidemiological evidence has identified significant developmental risk factors for major depression and anxiety disorders. The best documented is a history of physical or sexual abuse early in life, serious child neglect, or other early, severe stressors. Investigations of such early stressors have focused on possible roles for altered reactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Studies of early stress in animal models suggest that epigenetic regulation of gene expression may have a role in altering developmental trajectories. Such results cannot be readily followed up in humans because of lack of access to human brain tissue and thus remain hypothetical.

Other risk factors for depression and anxiety disorders include alcohol and other substance use disorders and the presence of other psychiatric disorders, such as attention deficit hyperactivity disorder, learning disorders, and obsessive-compulsive disorder. There is also evidence that alcoholism and other substance abuse disorders may be initiated by misguided attempts at self-medication of depression or anxiety, in turn worsening the underlying condition.

Environmental factors that may trigger new episodes of depression or anxiety include life transitions such as marriage, a new job, or retirement. Serious illness, whether acute or chronic, is also associated with the onset of major depression and anxiety. Some neurological disorders are associated with an elevated risk of depression, including Parkinson disease, Alzheimer disease, multiple sclerosis, and stroke. Some prescribed medications, such as interferons, also frequently trigger depression. When major depression accompanies a chronic illness such as type 2 diabetes or cardiovascular disease, the overall medical outcomes are worse, as a result of both the physiological

effects of depression, such as increased release of stress hormones (see below) and decreased motivation to engage in rehabilitative regimens.

Depression and Stress Share Overlapping Neural Mechanisms

Depression and responses to stress exhibit complex but significant interactions. As already noted, severe childhood adversity is a developmental risk factor for depression; moreover, depressive episodes may be initiated by a stressful experience. Conversely, the experience of depression is itself stressful because of the suffering it causes and its negative effects on functioning. Symptomatically, depression shares several physiological features with chronic stress, including changes in appetite, sleep, and energy. Both major depression and chronic stress are associated with persistent activation of the HPA axis (Figure 61–1).

Many but not all individuals with major depression and many in the depressed phase of bipolar disorder exhibit excess synthesis and secretion of the glucocorticoid stress hormone cortisol and the factors that regulate it, corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH). In a healthy state, a *transient* increase in cortisol secretion, as occurs in response to acute stress, shifts the body to a catabolic state (making glucose available to confront the stressor or threat), increases subjective energy levels, sharpens cognition, and may increase confidence. However, a *chronic* increase in glucocorticoids may contribute to depression-like symptoms. For example, many people with Cushing disease (in which pituitary tumors secrete excess ACTH, leading to excess cortisol) experience symptoms of depression.

Feedback mechanisms within the HPA axis normally permit cortisol (or exogenously administered glucocorticoids) to inhibit CRH and ACTH secretion and therefore to suppress additional cortisol synthesis and secretion. In approximately half of people with major depression, this feedback system is impaired; their HPA axis becomes resistant to suppression even by potent synthetic glucocorticoids such as dexamethasone. Although readily measurable disturbances of the HPA axis have not proven sensitive or specific enough to be used as a diagnostic test for depression, the observed abnormalities suggest strongly that a pathologically activated stress response is often an important component of depression.

The relationship of stress with depression has led to the development of several chronic stress paradigms in rodent models of depression. The reliance on

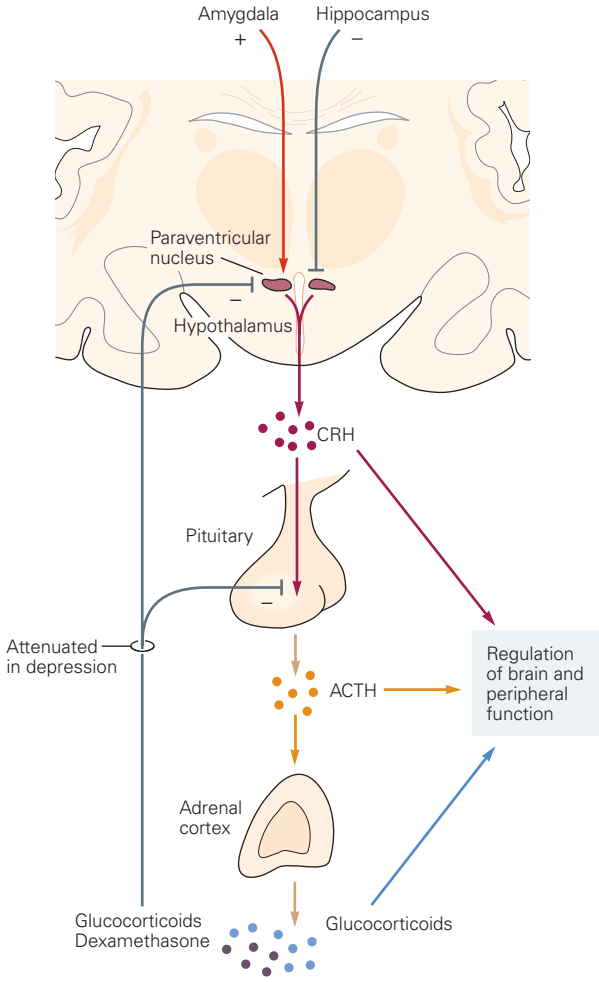

Figure 61–1 The hypothalamic-pituitary-adrenal axis. Neurons in the paraventricular nucleus of the hypothalamus synthesize and release corticotropin-releasing hormone (**CRH**), the key regulatory peptide in the hormonal cascade activated by stress. The CRH neurons have a circadian pattern of secretion, and the stimulatory effects of stress on CRH synthesis and secretion are superimposed on this basal circadian pattern. Excitatory fibers from the amygdala convey information about stressful stimuli that activates CRH neurons; inhibitory fibers descend from the hippocampus onto the paraventricular nucleus. CRH enters the hypophyseal portal system and stimulates the corticotropic cells in the anterior pituitary that synthesize and release adrenocorticotropic hormone (**ACTH**). The released ACTH enters the systemic circulation and stimulates the adrenal cortex to release glucocorticoids. In humans, the major glucocorticoid is cortisol; in rodents, it is corticosterone. Both cortisol and synthetic glucocorticoids such as dexamethasone act at the level of the pituitary and hypothalamus to inhibit further release of ACTH and CRH, respectively. The feedback inhibition by glucocorticoids is attenuated in major depression and the depressed phase of bipolar disorder. (Adapted, with permission, from Nestler et al. 2015.)