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Disorders of Mood and Anxiety

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An Overall View

Emotions are transient responses to specific stimuli in the environment (eg, the presence of danger), the body (eg, pain), or, for humans, the mind (eg, a train of thought). When an emotional state is prolonged, it can become one's dominant emotional state over time, or mood. Mood thus may be independent of immediate personal and environmental circumstances.

Mood and anxiety disorders are the most common serious disorders of the brain. Mood disorders generally involve either depression or elation. Anxiety disorders involve abnormal regulation of a powerful emotion, fear. In both mood and anxiety disorders the core symptoms have a major emotional component and are accompanied by physiological, cognitive, and behavioral abnormalities.

We discuss disorders of mood and anxiety together because both involve negative emotional states and because they appear to involve overlapping neural circuits that include the amygdala and the anterior cingulate cortex. There also is evidence for overlapping risk factors between major depressive disorder and some anxiety disorders. Commonalities of circuitry and genetic risks, as well as the negative effects of long-term anxiety on a person's mood, may explain the observation that nearly 60% of patients with major depressive disorder also suffer from an anxiety disorder. Anxiety disorder most commonly precedes the onset of depression.

Because emotions are transient responses to stimuli that can be reproduced in the laboratory, they have proven more amenable than moods to neuroscientific study. Objective measurement of moods is difficult,

compared with the more stereotypic physiological or behavioral components of emotional responses (see Chapter 48), and experimental approaches to regulating mood have had limited success. Good animal models exist for certain emotions, such as fear and pleasure, and because many features of these states appear to be conserved in evolution, the animal models are relevant to humans (see Chapter 48).

Animal models have allowed detailed investigation of the neural circuitry, physiology, and biochemistry underlying these states. For example, studies of rodent models of instinctive (unlearned) fear and learned fear (in which an animal learns to associate a previously neutral cue with a threat) have elucidated the "fear circuits" centered in the amygdala and the hypothalamus. These circuits activate the sympathetic nervous system to alter heart rate and blood pressure, stimulate secretion of stress hormones, and elicit species-specific defensive behaviors such as motionlessness ("freezing") in rodents and escape behaviors in other species. Such basic investigations are providing testable hypotheses for studies of fear and anxiety and their disorders in humans.

In contrast, neurobiological investigations of moods are less advanced. Although much evidence suggests that animals do have moods, developing empirical methods of ascertaining what those moods are and how they match human experience has been challenging. Most animal models of depression were not developed to investigate the pathophysiology of the human disease, but as empirical screens for antidepressant drugs. Many of these models are based on chronic stress; although chronic stress and depressed mood have many features in common, they are not identical.

The lack of well-validated animal models of moods and mood disorders has made it difficult to identify the neural circuitry responsible for the regulation and maintenance of moods. Much investigation of mood circuitry has perforce been carried out in humans using noninvasive technologies such as neuro-imaging.

The Most Common Disorders of Mood Are Unipolar Depression and Bipolar Disorder

In the 5th century BC moods were thought to depend on the balance of four humors—blood, phlegm, yellow bile, and black bile. An excess of black bile was believed to cause depression. In fact, the ancient Greek term for depression, *melancholia,* means black bile. Although this explanation of depression seems fanciful today, the underlying view that psychological disorders reflect physical processes is correct.

Only in the past three decades have relatively precise criteria for mood disorders been developed in parallel with those for thought and cognitive disorders (see Chapter 61). Disorders of mood are now classified based on symptoms, natural history (including age of onset, course, and outcome), patterns of familial transmission, and response to treatment. Based on these factors, one can distinguish between two major classes of disorders in people who suffer from depression. Unipolar depression is diagnosed in people who suffer only from depressive episodes; bipolar disorder is diagnosed in individuals in whom depression alternates with episodes of mania (Table 63–1).

Another important distinction is that between primary and secondary mood disorders. Mood disorders caused by drugs (eg, drugs used to treat hypertension) or pathophysiological processes that affect the brain (eg, hypothyroidism) are considered secondary to another condition. The onset of depression late in life also may be secondary to pathophysiological processes such as Parkinson disease or diffuse vascular disease affecting cerebral vessels. Although such cases are important, our discussion here focuses on mood disorders, unipolar and bipolar illnesses, arising as independent pathophysiological processes.

Unipolar Depression Often Begins Early in Life

The key clinical features of unipolar depression can be summarized in Hamlet's words, "How weary, stale, flat, and unprofitable seem to me all the uses of this world!" Untreated, an episode of depression typically lasts 4 to 12 months. The central feature of depression is an unpleasant (dysphoric) mood present most of the day, day in and day out, often accompanied by intense mental anguish, the inability to experience pleasure (anhedonia), and a generalized loss of interest in the world. Sadness is most typical, but anger, irritability, and loss of interest in usual pursuits can predominate in some patients.

Major depression is distinguished from normal sadness or grief by its severity, pervasiveness, duration, and associated symptoms, including physiological, behavioral, and cognitive symptoms (Table 63–1). Physiological symptoms include sleep disturbance, most often insomnia with early morning awakening, but occasionally excessive sleeping; loss of appetite and weight loss, but occasionally excessive eating; and decreased energy. Behaviorally, some depressed patients exhibit slowed motor movements, described

Table 63–1 Symptoms of Mood Disorders

Major Depression

A. Either depressed mood (1) or loss of interest or pleasure (2):
1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, "I feel sad or empty") or observation made by others (eg, "He 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)

B. At least four of the following symptoms are present nearly every day for at least 2 weeks:
1. Significant weight loss when not dieting, or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
2. Insomnia or hypersomnia nearly every day
3. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
4. Fatigue or loss of energy nearly every day
5. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
6. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
7. 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

Manic Episode

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

B. During the period of mood disturbance three (or more) of the following symptoms have persisted (four if the mood is only irritable) 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
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)

Adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.

as psychomotor retardation, whereas others can be extremely agitated. Cognitive symptoms are evident in both the content of thoughts (hopelessness, thoughts of worthlessness and of guilt, suicidal thoughts and urges) and in cognitive processes (difficulty concentrating, slow thinking, and poor memory).

In the most severe forms of depression psychotic symptoms can occur, including delusions (unshakable false beliefs that cannot be explained by a person's culture) and hallucinations. The psychotic symptoms of depression generally reflect the person's feelings that he or she is worthless or bad. A severely depressed person might, for example, believe that he or she is emitting a potent odor because he or she is rotting from the inside.

The most serious negative outcome from depression is suicide. Suicide is the eighth leading cause of death in the United States, and the third leading cause of death among young people 15 to 24 years of age. More than 90% of suicides are associated with mental illness, with depression being the leading cause.

In the standard classification of psychiatric disorders in the United States—the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) of the American Psychiatric Association—episodic, primary, unipolar depression that lasts for at least two weeks is classified as major depression. Major depression often begins early in life; approximately one-half of cases occur in those younger than 25 years of age, but first episodes are observed across the life span. Those who have had a first episode in childhood or adolescence have a particularly high likelihood of recurrence. Once a second episode has occurred, a pattern of

repeated relapse and remission generally sets in. Some people do not recover completely from their first acute episode and have chronic, albeit milder, unremitting depression that can be punctuated by acute exacerbations. Chronic, somewhat milder depressions lasting more than 2 years are called *dysthymia*. Although the symptoms of dysthymia are less severe than those of a major depressive episode, the long duration of the symptoms makes this a very disabling illness.

Bipolar Disorder Includes Episodes of Mania

Bipolar disorder is named for its chief symptom, swings of mood between mania and depression. Mania is characterized by euphoria or irritability, a marked increase in energy and a decreased need for sleep, impulsiveness, and excessive engagement in goal-directed behaviors, often with poor judgment characterized by extreme optimism. For example, a person might go on spending sprees well beyond his or her means. During manic episodes self-esteem is inflated, often reaching delusional proportions; individuals might consider themselves to be royalty, prophets, or even deities.

Mania also affects cognition. During a manic episode a person often cannot stick to a topic and might jump quickly from idea to idea, making comprehension difficult. Speech is typically rapid and difficult to interrupt. Psychotic symptoms commonly occur during manic episodes and are generally consistent with the person's elevated mood. For example, people with mania can have delusions that they possess special powers. The symptoms that characterize the depressive episodes in bipolar disorder are indistinguishable from those in unipolar depressions.

Patients who have had at least one manic episode are considered to have bipolar disorder, even if they have not yet experienced a depressive episode. The onset of manic episodes tends to be relatively rapid, occurring over a period of a few days to a few weeks. Bipolar disorder generally begins in young adulthood, uncommonly in childhood. Most episodes lack a clear precipitant, but sleep deprivation can initiate a manic episode, suggesting a relationship between neural systems that regulate circadian rhythms and those that regulate moods. People with bipolar disorder have recurrent episodes of the illness, both manias and depression. However, the rate of cycling between mania, depression, and normal mood (euthymia) varies widely. Between periods of mania or depression some people with bipolar disorder are relatively free of symptoms, but a large fraction have residual symptoms. A few patients have severe, chronic symptoms despite treatment.

Mood Disorders Are Common and Disabling

The lifetime risk of major depressive disorder in the United States is 16.2%. Within any 1 year 6.6% of the population suffers major depression. The prevalence of depression differs in different countries and cultures, but the nature of the symptoms is remarkably similar around the world.

In childhood major depression occurs equally in males and females. After puberty, however, depression occurs more commonly in females independent of culture. In the United States the ratio of females to males with major depression is 1.7:1. Depression is the leading cause of disability worldwide.

In contrast to the high frequency of unipolar depression, bipolar disorder is less common, with a prevalence of 1% that exhibits relatively little variability from country to country. As with major depression, the symptoms are the same across countries and cultures. The risk of bipolar disorder is equivalent in males and females worldwide.

Both Genetic and Nongenetic Risk Factors Play an Important Role in Mood Disorders

As with schizophrenia, both bipolar disorder and major depression run in families with patterns of transmission that are inconsistent with simple Mendelian (single gene) dominant, recessive, or sex chromosome-linked modes of inheritance. One way to estimate the influence of genes on a disease phenotype is to measure the increased risk that results from relatedness to a person who has the disease. This increase in risk can be expressed as a *recurrence risk ratio.* The recurrence risk ratio provides a rough measure of the aggregate influence of genes on a trait but does not provide insight into how many genes might be involved.

Recurrence risk ratios demonstrate that genes contribute to the risk of unipolar depression but exert a much stronger influence on the risk of bipolar disorder (Table 63–2). As in schizophrenia (see Chapter 62), the concordance rates among monozygotic twin pairs (who are genetically identical) are less than 100%. Thus genes alone do not cause mood disorders but must interact with developmental or environmental factors to produce illness.

Overall the genetic risk for mood disorders, like that for schizophrenia, is genetically complex. Genetic linkage and association studies suggest there are multiple pathways of genetic risk for mood disorders, and thus no single gene will likely prove to be either necessary or sufficient.

Table 63–2 Recurrence Risk Ratios (λ) for Mood Disorders and Schizophrenia

Disorder	Siblings	Identical twins
Schizophrenia	9	48
Bipolar disorder	7	60
Major depression	2–3	16

λ measures the lifetime risk for a disorder as a multiple of the general population risk that results from the degree of relatedness to a person with the disorder. Thus for schizophrenia the base rate in the population is 1%. Given a sibling with schizophrenia there is a ninefold increase in risk (which in this case equals a 9% risk). Given an identical twin with the disorder, the relative risk is 48 times higher than in the general population. Schizophrenia and bipolar disorder are highly genetically influenced, major depression more moderately so.

From the point of view of prevention it is important to sort out the relative roles of genes and environmental risk factors because the latter can be modified. Much evidence suggests that stressful and adverse life events increase the risk of major depression; even here, however, genes may play a role in two ways because they shape a person's temperament. First, temperament plays a role in the kinds of situations into which people place themselves; second, genetic factors can influence the response that people have to adverse life experiences when they do occur. Such interactions between genetic and environmental factors complicate the task of isolating risk factors.

Specific Brain Regions and Circuits Are Involved in Mood Disorders

Because animal models of mood and mood regulation are not fully convincing, investigation of the circuitry involved in mood disorders has relied to a great extent on structural and functional imaging of humans, and to a lesser degree on postmortem analyses of human brains. Neuro-imaging studies of major depression and bipolar disorder have identified abnormalities in brain regions thought to be involved in emotion and cognition (Figure 63–1). Despite progress to date, imaging has not yet identified specific abnormalities in a neural system that can be used reliably to diagnose major depressive or bipolar disorder.

One brain region that has consistently been implicated in both major depressive and bipolar disorders is the gyrus of the anterior cingulate cortex. This structure runs parallel to the corpus callosum, along the medial surface of each cerebral hemisphere (Figure 63–1). It has two functional subdivisions. A rostral and ventral subdivision is thought to be involved in emotional processes and autonomic function; it has extensive connections to the hippocampus, the amygdala, orbital prefrontal cortex, anterior insula, and nucleus accumbens. A caudal subdivision is thought to be involved in cognitive processes and the control of behavior; it connects with the dorsal regions of prefrontal cortex, secondary motor cortex, and posterior cingulate cortex.

Abnormal function in both subdivisions of the anterior cingulate cortex has been documented in people with mood disorders (Figure 63–2). However, abnormal functioning during major depressive episodes and the depression phase of bipolar disorder has been most consistently found in the rostral subdivision, which is concerned with emotion, and especially in the subgenual region (the region ventral to the genu of the corpus callosum). Indeed, a decrease in activity of the subgenual anterior cingulate gyrus following antidepressant treatment correlates with the success of the treatment (Figure 63–3).

Neuro-imaging also implicates the amygdala and hippocampus in mood disorders. The involvement of the amygdala is not surprising given the wealth of evidence that this structure is involved in the processing of negative emotions, including fear (see Chapter 48). Enlargement of the amygdala has been found in depression, and increases in the basal level of activity in the amygdala have been observed in depression, bipolar disorder, and anxiety disorders. As in many disorders, the volume of the hippocampus may be reduced in depression. This change correlates with the duration of prior episodes of depression and not with the age of the person, consistent with the idea that protracted major depression might produce hippocampal atrophy. Nonetheless, until longitudinal studies are conducted we cannot be certain whether a small hippocampus is a risk factor for depression or a result of it.

Despite the findings that we have described, the use of neuro-imaging to study depression is still in its early stages. Most studies to date have been restricted to anatomical measurement of brain structures or to basal (unstimulated) brain activity in depressed subjects compared with healthy control subjects. Investigators are now beginning to use *activation paradigms*, in which brain activity is measured in response to specific cognitive or emotional stimuli.

Activation paradigms can be a powerful means of identifying brain circuits associated with specific normal and disordered function. For example, in healthy

subjects the anterior cingulate cortex is activated by pain, cognitive conflict, and errors in task performance. Thus the anterior cingulate cortex may ascertain whether behavior is successfully proceeding toward desired goals, and perceived discrepancies between goals and outcomes could contribute to depression.

Depression and Stress Are Interrelated

In some cases depression follows a stressful experience; conversely, the experience of depression is itself stressful. Indeed, depression shares several features with chronic stress, including changes in appetite, sleep, and energy. Major depression and chronic stress may also share biochemical changes, such as persistent activation of the hypothalamic-pituitary-adrenal (HPA) axis (Figure 63–4).

In depressed individuals daily production of the glucocorticoid stress hormone cortisol and secretion of corticotrophin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) can all be elevated. A *transient* increase in cortisol secretion, as occurs with acute stress, suppresses the immune system (saving energy and delaying inflammatory processes that might inhibit the fight-or-flight response), shifts the body to a catabolic state (making energy available to confront the cause of the stress), increases energy levels, sharpens cognition, and may increase confidence. However, a *chronic* increase may contribute to symptoms of depression. For example, people with Cushing disease (in which pituitary tumors secrete excess ACTH leading to excess cortisol) often experience depression and insomnia.

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 one-half of people with major depression this feedback system

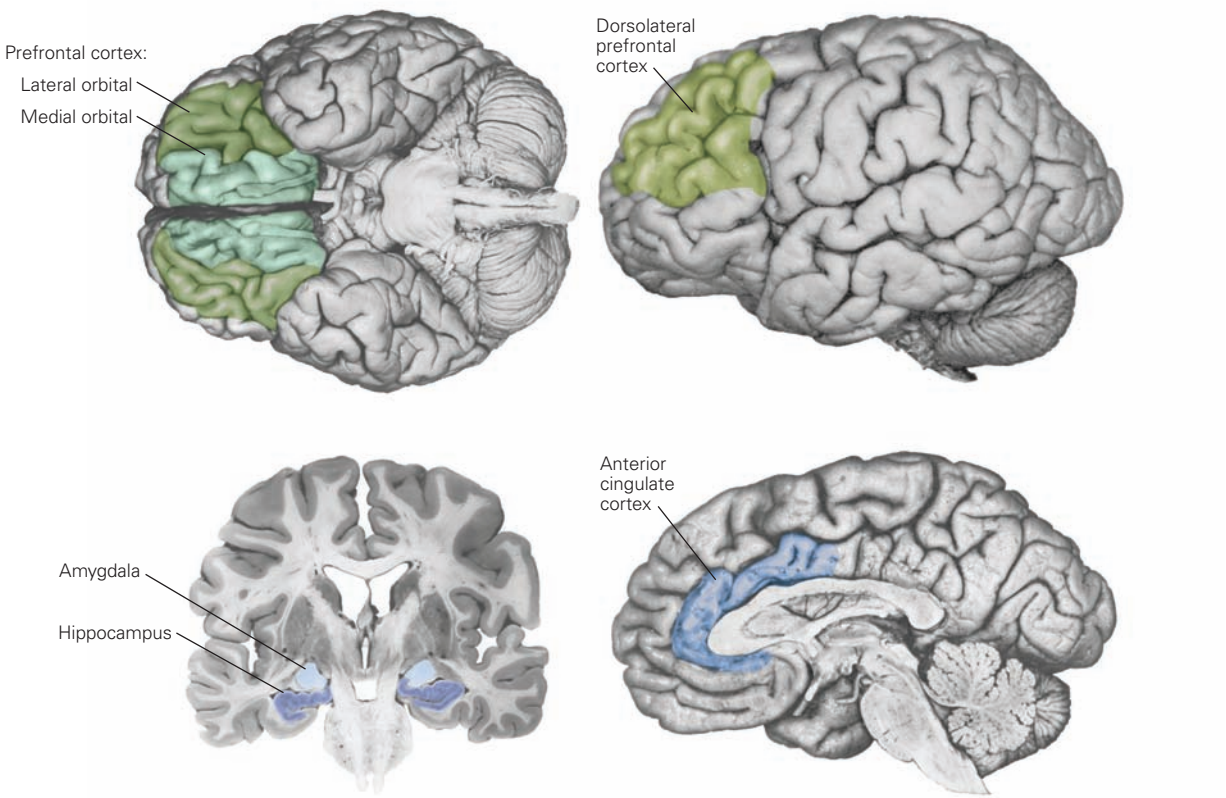

Figure 63–1 Brain centers of emotional dysfunction in patients with depression. Each of these interconnected structures plays a role in regulating emotion and physiological and behavioral responses to emotional stimuli. Abnormalities in one or more of these regions or in the interconnections among them are associated with failures of emotion regulation. (Reproduced, with permission, from Davidson, Putnam, and Larson 2000.)

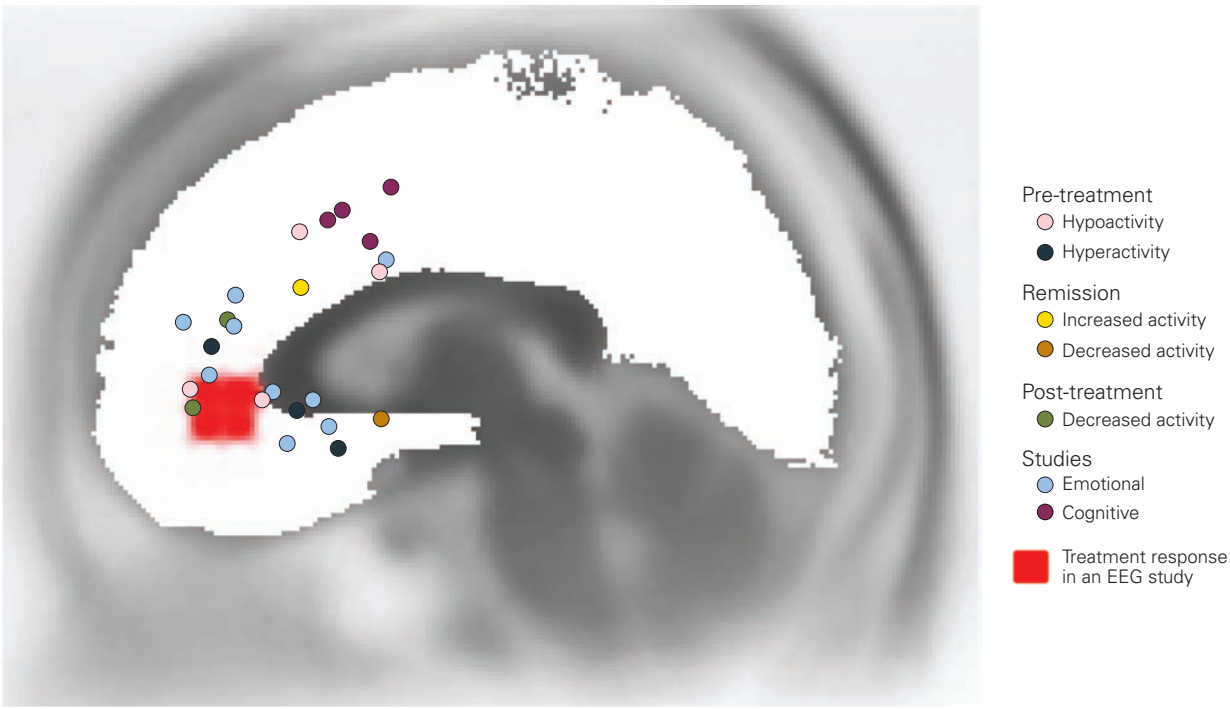

Figure 63–2 Involvement of the anterior cingulate cortex in depression. The figure summarizes the findings of several studies using brain imaging. Colored circles show sites of activation or deactivation before or after treatment of patients with depression. **Black circles** indicate pretreatment hyperactivity among patients who responded to treatment; **green circles** indicate posttreatment decreased activity in responders; **pink circles** indicate hypoactivity in depressed subjects; **yellow circles** indicate increased activity with remission of depression; and the sole **brown circle** indicates decreased activity with remission of depression. Studies involving emotional tasks (**blue circles**) and cognitive tasks (**purple circles**) in nonpsychiatric subjects are also shown. The large **red area** shows the location of treatment response observed in an electroencephalogram (EEG) study of depression. (Adapted, with permission, from Pizzagalli et al. 2001.)

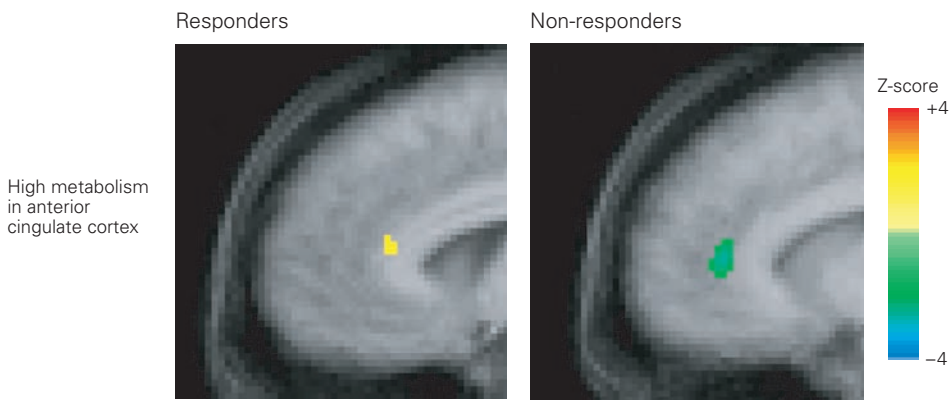

Figure 63–3 Increased activity in the anterior cingulate cortex predicts responsiveness to treatment with antidepressant drugs. Regional cerebral glucose metabolism was measured by positron emission tomography (PET) as a proxy for brain activity. Depressed patients with elevated metabolism in the rostral anterior cingulate cortex had better responses to antidepressant treatment than those who did not. Cingulate hypermetabolism may represent an adaptive response to depression that predicts antidepressant response. (Reproduced, with permission, from Mayberg et al. 1997).

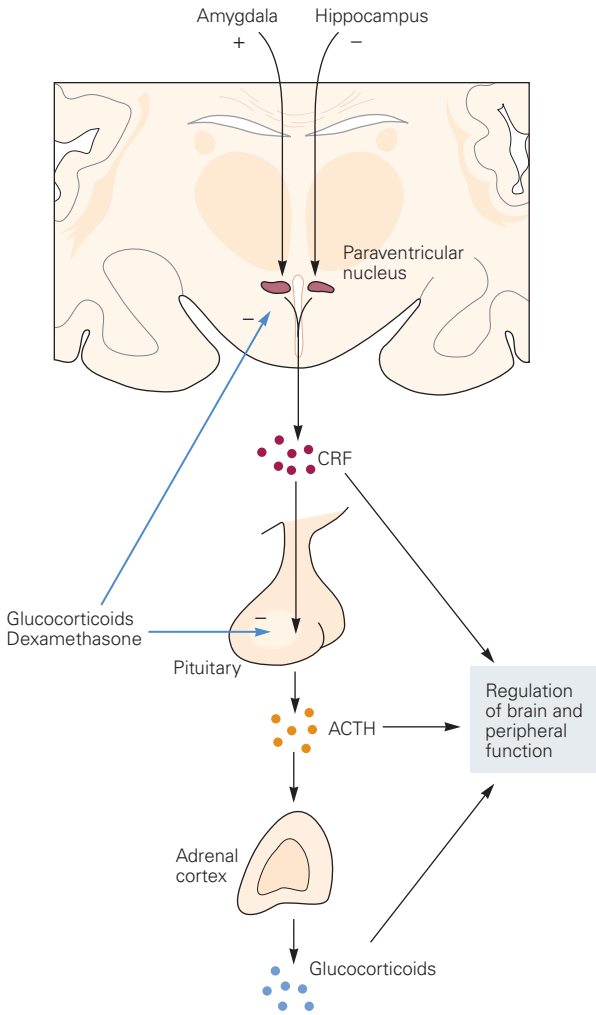

Figure 63–4 The hypothalamic-pituitary-adrenal axis. Neurons in the paraventricular nucleus of the hypothalamus synthesize and release corticotropin-releasing factor (**CRF**), the key regulatory hormone in this cascade. Secretion of CRF follows a circadian pattern, and the effects of stress are superimposed on this circadian pattern. Excitatory fibers from the amygdala convey information about stress and activate CRF secretion and biosynthesis; inhibitory fibers descend from the hippocampus. CRF enters the hypophyseal portal system and stimulates the corticotrophic cells of the anterior pituitary. These cells synthesize and release adrenocorticotropic hormone (**ACTH**), which enters the systemic circulation and ultimately 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 CRF respectively. (Adapted, with permission, from Nestler, Hyman, and Malenka 2009.)

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 are not sensitive or specific enough to be used as a diagnostic test for depression, the observed abnormalities suggest strongly that altered stress responses are an important component of depression in a large proportion of people with the illness.

If recurrent depression causes the decrease in hippocampal volumes described above, it may be that excessive cortisol secretion is the cause. Two theories have been offered to explain how depression might lead to hippocampal atrophy. One is that persistently elevated levels of glucocorticoids can damage mature neurons, perhaps making them more susceptible to glutamate excitotoxicity (see Chapter 43). The other is that elevated cortisol levels or some other aspect of chronic stress suppresses normal neurogenesis (the formation of new neurons), resulting in fewer cells being produced and thus a smaller hippocampus.

In many animals, as well as humans, new granule cells within the dentate gyrus of the hippocampus are produced during adult life. In rodents these new neurons are incorporated into neural circuits. Stressful or aversive experiences as well as glucocorticoids inhibit the proliferation of granule cell precursors and thus suppress normal rates of neurogenesis in the hippocampus. In contrast, antidepressants, including the selective serotonin reuptake inhibitors, increase the rate of neurogenesis. Thus depression might cause hippocampal atrophy by inhibiting neurogenesis and antidepressants might reverse this effect by treating the depression (therefore decreasing stress) and possibly by directly stimulating neurogenesis (by mechanisms that are not yet understood).

These hypothalamic and hippocampal abnormalities may contribute to the symptoms of depression and influence its course. Hypothalamic CRH secretion is under the stimulatory control of pathways from the amygdala and inhibitory pathways from the hippocampus. Damage to the hippocampus could lead to a vicious cycle in which loss of inhibitory control of CRH secretion would lead to greater cortisol release, producing additional hippocampal atrophy. In fact, depression can be accompanied by memory impairments that could be explained by hippocampal dysfunction, either by itself or in conjunction with disturbances in executive function involving the prefrontal cortex, such as failure of attentional mechanisms at the time of memory encoding.

Major Depression Can Be Treated Effectively

Three types of treatment are effective for major depressive disorder: antidepressant drugs, cognitive-behavioral psychotherapy, and electroconvulsive therapy.

Antidepressant Drugs Target Monoaminergic Neural Systems

The most widely used treatment for depression is antidepressant drugs that act initially on the monoaminergic systems in the nervous system. The monoamines—serotonin, norepinephrine, and dopamine—are synthesized in small nuclei within the brain stem (see Figure 46–2). Serotonergic and noradrenergic nuclei are concentrated in the caudal brain stem (Figures 63–5 and 63–6). Most dopamine in the brain is synthesized in more rostral nuclei, the substantia nigra and ventral tegmental area of the midbrain (see Figure 46–2E). Each of the monoaminergic nuclei projects widely throughout the brain; the serotonergic and noradrenergic axons descend into the spinal cord as well. This widespread connectivity permits monoaminergic neurons to produce coordinated responses and thus to influence functions such as arousal, attention, vigilance, motivation, and other cognitive and emotional states that involve multiple brain regions.

Serotonin, norepinephrine, and dopamine are synthesized from amino acid precursors and either packaged into synaptic vesicles for release (see Chapter 12) or else metabolized by the enzyme monoamine oxidase (MAO), which is associated with the outer leaflet of mitochondrial membranes. After release these neurotransmitters bind synaptic receptors or are cleared

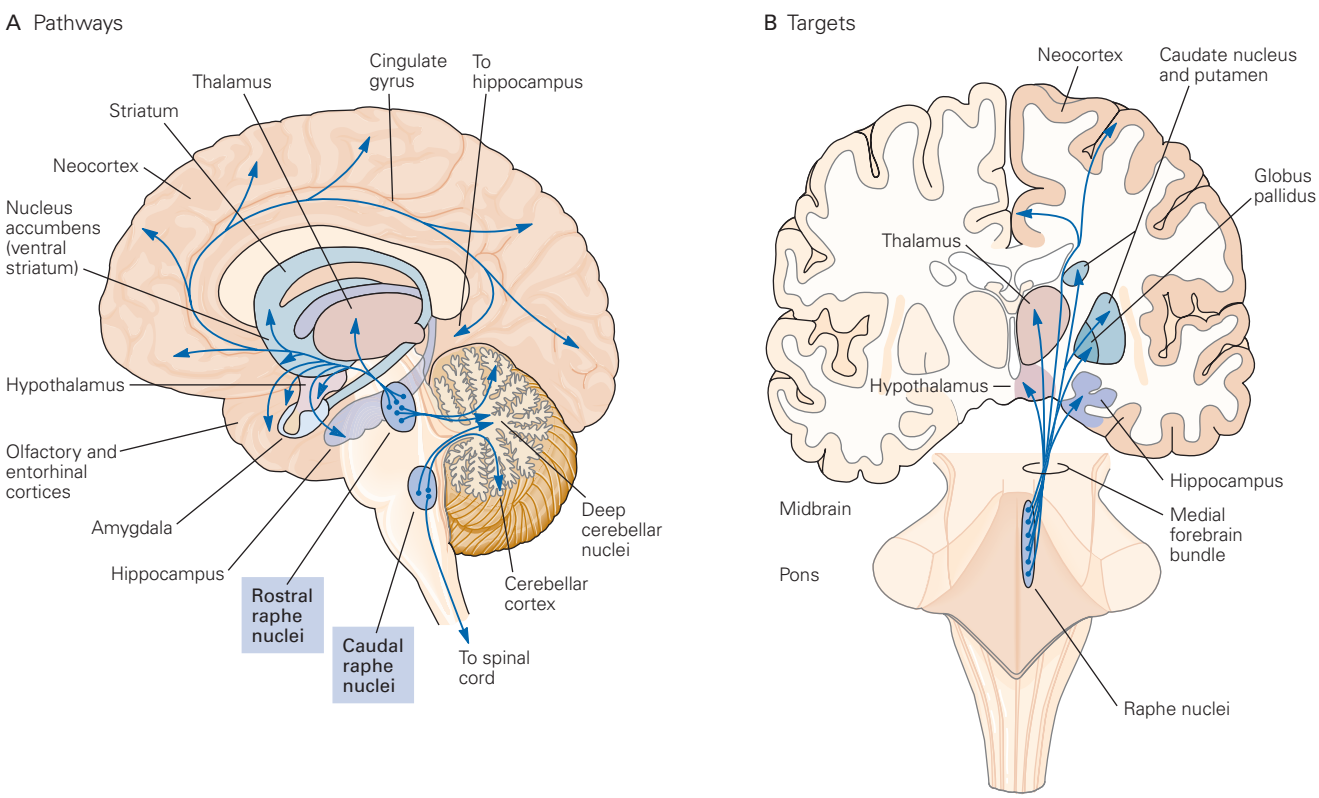

Figure 63–5 The major serotonergic systems in the brain arise in the raphe nuclei of the brain stem. Serotonin is synthesized in a group of brain stem nuclei called the raphe nuclei. These neurons project throughout the neuraxis, ranging from the forebrain to the spinal cord. The serotonergic projections are the most massive and diffuse of the monoaminergic systems, with single serotonergic neurons innervating hundreds of target neurons. (Adapted, with permission, from Heimer 1995.)

A. A sagittal view of the brain illustrates the raphe nuclei. In the brain these nuclei form a fairly continuous collection of cell groups close to the midline of the brain stem and extending along its length. In the drawing here they are shown in more distinct rostral and caudal groups. The rostral raphe nuclei project to a large number of forebrain structures.

B. This coronal view of the brain illustrates some of the major structures innervated by serotonergic neurons of the raphe nuclei.

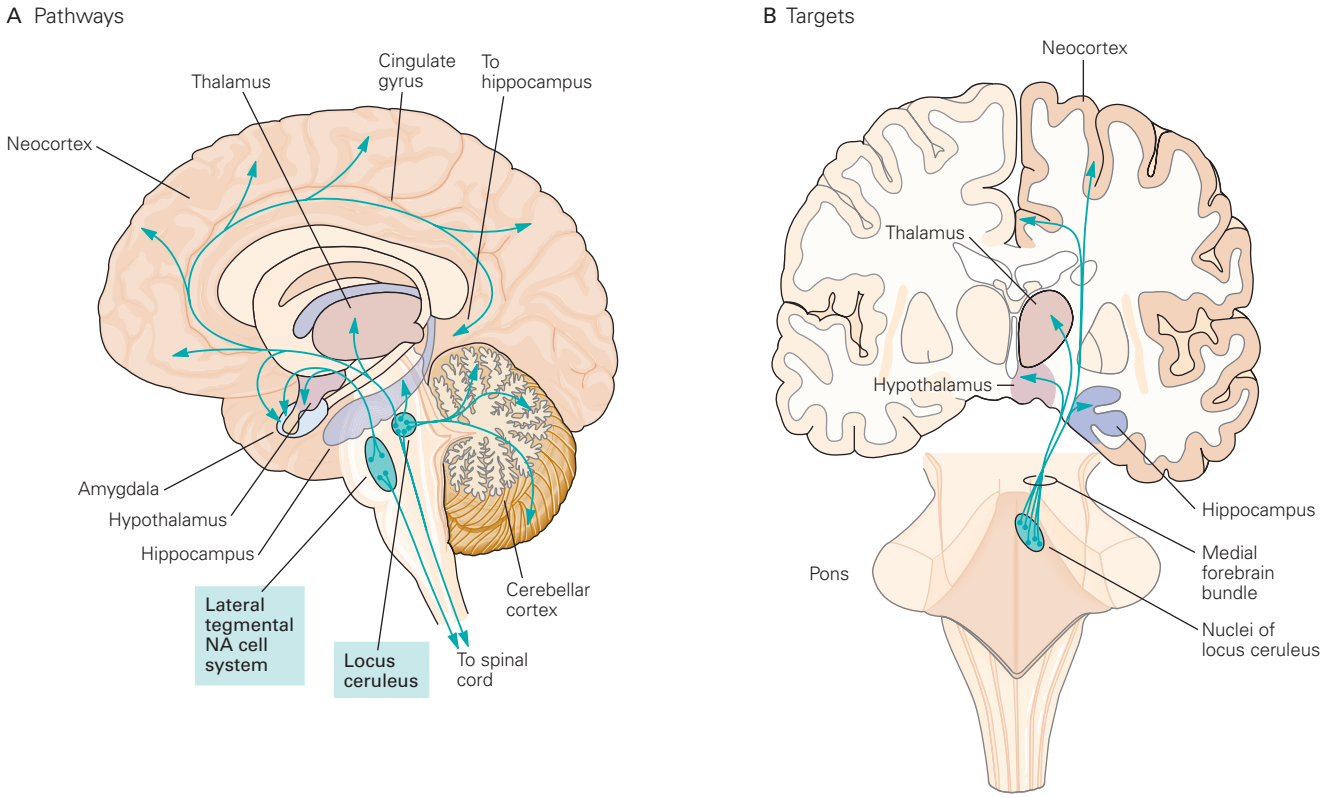

Figure 63–6 The major noradrenergic projection of the forebrain arises in the locus ceruleus. (Adapted, with permission, from Heimer 1995.)

A. Norepinephrine is synthesized in several brain stem nuclei, the largest of which is the nucleus locus ceruleus, a pigmented nucleus located just beneath the floor of the fourth ventricle in the rostrolateral pons. A lateral midsagittal view demonstrates the course of the major noradrenergic pathways from the locus ceruleus and lateral brain stem tegmentum. Axons from the locus ceruleus project rostrally into the forebrain and also into the cerebellum and spinal cord; axons from noradrenergic nuclei in the lateral brain stem tegmentum project to the spinal cord, hypothalamus, amygdala, and ventral forebrain.

B. A coronal section shows the major targets of neurons from the locus ceruleus.

from the synapse by specific transporters located on the presynaptic cell membrane.

Serotonin and norepinephrine each have a variety of receptors on the presynaptic terminals as well as postsynaptic target cells. There are at least 14 distinct serotonin receptors in humans, divided into seven major classes denoted 5-HT_1 through 5-HT_7 (Table 63–3). Norepinephrine receptors can be divided into two major classes, the α and β adrenergic receptors, with multiple subtypes (Table 63–4). With the exception of the 5-HT_3 receptor, serotonin, norepinephrine, and dopamine act on G protein-coupled receptors that initiate signaling cascades that produce long-term changes in the response properties of the postsynaptic neuron. It is thought that antidepressant drugs are able to alter the responsiveness of the brain to diverse cognitive and emotional stimuli by directly or indirectly influencing G protein-coupled receptors expressed in large numbers of neurons.

The most widely used antidepressant drugs fall into several major groupings, each of which affects the monoaminergic systems in different ways (Figure 63–7). The *monoamine oxidase inhibitors,* such as phenelzine and tranylcypromine, were the first effective antidepressants. They are highly effective against both depression and anxiety disorders but are rarely used today because of their side effects. MAO inhibitors may exert their effects on depression by blocking the capacity of MAO to break down norepinephrine, serotonin, or dopamine in presynaptic terminals, thus making extra neurotransmitter available for packaging into vesicles and for release.

Two forms of MAO, types A and B, are found in the brain. Type A is also found in the gut and liver,

Table 63–3 Serotonin Receptors

Receptor	G-Protein linkage	Locations in the brain
5-HT_{1A}	$G_{i/o}$	Cerebral cortex, hippocampus, septum, amygdala, dorsal raphe
5-HT_{1B}	$G_{i/o}$	Substantia nigra, basal ganglia
5-HT_{1D}	$G_{i/o}$	Substantia nigra, striatum, nucleus accumbens, hippocampus
5-HT_{1E}	$G_{i/o}$	Cerebral cortex, dorsal raphe, hippocampus
5-HT_{1F}	$G_{i/o}$	Cerebral cortex, dorsal raphe, hippocampus
5-HT_{2A}	$G_{q/11}$	Cerebral cortex, basal ganglia
5-HT_{2B}	$G_{q/11}$	No brain expression
5-HT_{2C}	$G_{q/11}$	Basal ganglia, substantia nigra, hippocampus
5-HT_3	Ligand-gated channel	Cerebral cortex, hippocampus, brain stem, spinal cord
5-HT_4	G_s	Striatum, nucleus accumbens, hippocampus
5-HT_{5A}	G_s	Cerebral cortex, hippocampus, cerebellum
5-HT_{5B}	Unknown	Cerebral cortex, hippocampus, cerebellum
5-HT_6	G_s	Cerebral cortex, striatum, olfactory tubercle, hippocampus
5-HT_7	G_s	Cerebral cortex, hypothalamus, thalamus

where it catabolizes bioactive amines that are present in foods. Inhibition of MAO-A permits bioactive amines such as tyramine to enter the bloodstream from foods that contain it in high concentrations, such as aged cheeses. These amines are taken up by sympathetic neurons through transporters, thus displacing endogenous monoamines. This process may result in massive release of norepinephrine and epinephrine, resulting in severe elevations of blood pressure. The MAO inhibitors that have been most widely used as antidepressants inhibit MAO-A and MAO-B nonselectively or MAO-A alone, and thus require that patients

Table 63–4 Norepinephrine Receptors

Receptor	G-Protein linkage	Locations in the brain
α_{1A}	$G_{q/11}$	Cerebral cortex, hippocampus
α_{1B}	$G_{q/11}$	Cerebral cortex, brain stem
α_{1D}	$G_{q/11}$	No brain expression
α_{2A}	$G_{i/o}$	Cerebral cortex, midbrain, caudal brain stem, spinal cord
α_{2B}	$G_{i/o}$	Diencephalon
α_{2C}	$G_{i/o}$	Cerebral cortex, basal ganglia, cerebellum, hippocampus
β_1	G_s	Cerebral cortex, cerebellar nuclei, brain stem, spinal cord
β_2	G_s	Hippocampus, piriform cortex, cerebellar cortex
β_3	$G_s/G_{i/o}$	No brain expression

avoid foods with a high monoamine content. A selective MAO-B inhibitor, selegiline, which has been used to treat Parkinson disease, has recently proved effective in treating depression. But at antidepressant doses, which are higher than for Parkinson disease treatment, it loses its selectivity.

The *tricyclic antidepressants*, such as imipramine, amitriptyline, and desipramine, inhibit either norepinephrine or serotonin transporters or both. These drugs are effective against depression and many anxiety disorders. But they also block many other neurotransmitter receptors, including the muscarinic acetylcholine, histamine H-1, and α_1 noradrenergic receptors, producing side effects such as dry mouth, drowsiness, urinary retention, and postural hypotension, thus limiting their use. Some newer drugs, such as venlafaxine and duloxetine, block both norepinephrine and serotonin but lack the tricyclic structure and the unwanted receptor interactions of the older drugs.

The *selective serotonin reuptake inhibitors*, such as fluoxetine, sertraline, and paroxetine, are widely used. As their name implies, they inhibit the uptake of serotonin selectively. They are effective for major depressive disorder, many anxiety disorders, and, in high doses, for obsessive-compulsive disorder.

In addition to their role in the pharmacologic treatment of mood disorders, the monoamine neurotransmitters may also play a role in pathogenesis. However, much of the evidence for such a link has come from the actions of antidepressant drugs themselves. Because effective treatments may exert their beneficial effects indirectly, the role of monoamines in pathogenesis remains quite uncertain.

Interest in the monoamines began in the 1950s when it was observed that reserpine, an alkaloid derived from the rauwolfia plant, then used to treat hypertension, precipitated depression in approximately 15% of people who received the drug. Reserpine depletes the brain of norepinephrine, serotonin, and dopamine by blocking the ability of presynaptic neurons to take up these neurotransmitters into synaptic vesicles. As a result, the neurotransmitters remain in the cytoplasm where they are degraded by monoamine oxidase. In a serendipitous discovery, iproniazid, a drug that was initially developed to treat tuberculosis, was found to have antidepressant properties. Because of its side effects, iproniazid itself is no longer in use, but it proved to be the prototype MAO inhibitor.

Because depression could be induced by reserpine, which depletes monoamines, and could be ameliorated by MAO inhibitors, which protects monoamines from degradation, the idea emerged that depression involved a decrease in the availability of monoamines. Further support for this idea came from the discovery of tricyclic antidepressants, which block the uptake of synaptically released norepinephrine and serotonin, thereby prolonging the action of these neurotransmitters within the synapse. These observations led to the hypothesis that depression results from a deficiency of monoaminergic synaptic transmission and that clinically effective antidepressants work by increasing the availability of monoamines at synapses.

A major weakness with this simple hypothesis comes from the observation that the inhibitory actions of antidepressants on monoamine uptake or on MAO are rapid and occur even with the first dose of medication, whereas several weeks of treatment are required to observe a lifting of the depression clinically. Attempts to explain this delay have led to several ideas. Enhancement of serotonergic or noradrenergic synaptic transmission stimulates a large number of pre- and postsynaptic receptors and activates downstream signaling pathways, some of which activate gene expression and ultimately protein synthesis. One general hypothesis is that, over weeks, newly synthesized proteins alter the responsiveness of neurons or cause the remodeling of synaptic connections in a manner that treats the depression. However, this hypothesis is not supported by any evidence of the genes and proteins that might be responsible or the cells and circuits in which they might exert their effects. One recently discovered mechanism by which antidepressants can regulate gene expression is by causing covalent modification of histone proteins and thus the conformation of chromatin. This type of mechanism might also contribute to the ability of antidepressant responses to persist even after treatment has been completed.

An additional hypothesis is based on the observation, described above, that antidepressant drugs enhance the rate of neurogenesis in the dentate gyrus of the hippocampus. According to this hypothesis the therapeutic delay in antidepressant response would result from the slow time course of development of new neurons and their incorporation into circuits. Some experiments suggest that inhibition of neurogenesis blocks the action of antidepressants in some rodent models of stress, but other experiments suggest that even if hippocampal neurogenesis plays a role in antidepressant action, it is not absolutely necessary.

The slow onset of existing antidepressant drugs is not only a scientific puzzle but also a serious clinical problem. While waiting for their symptoms to improve patients may become demoralized and a minority may be at increased risk of suicidal thoughts and acts. The search for rapidly acting antidepressants

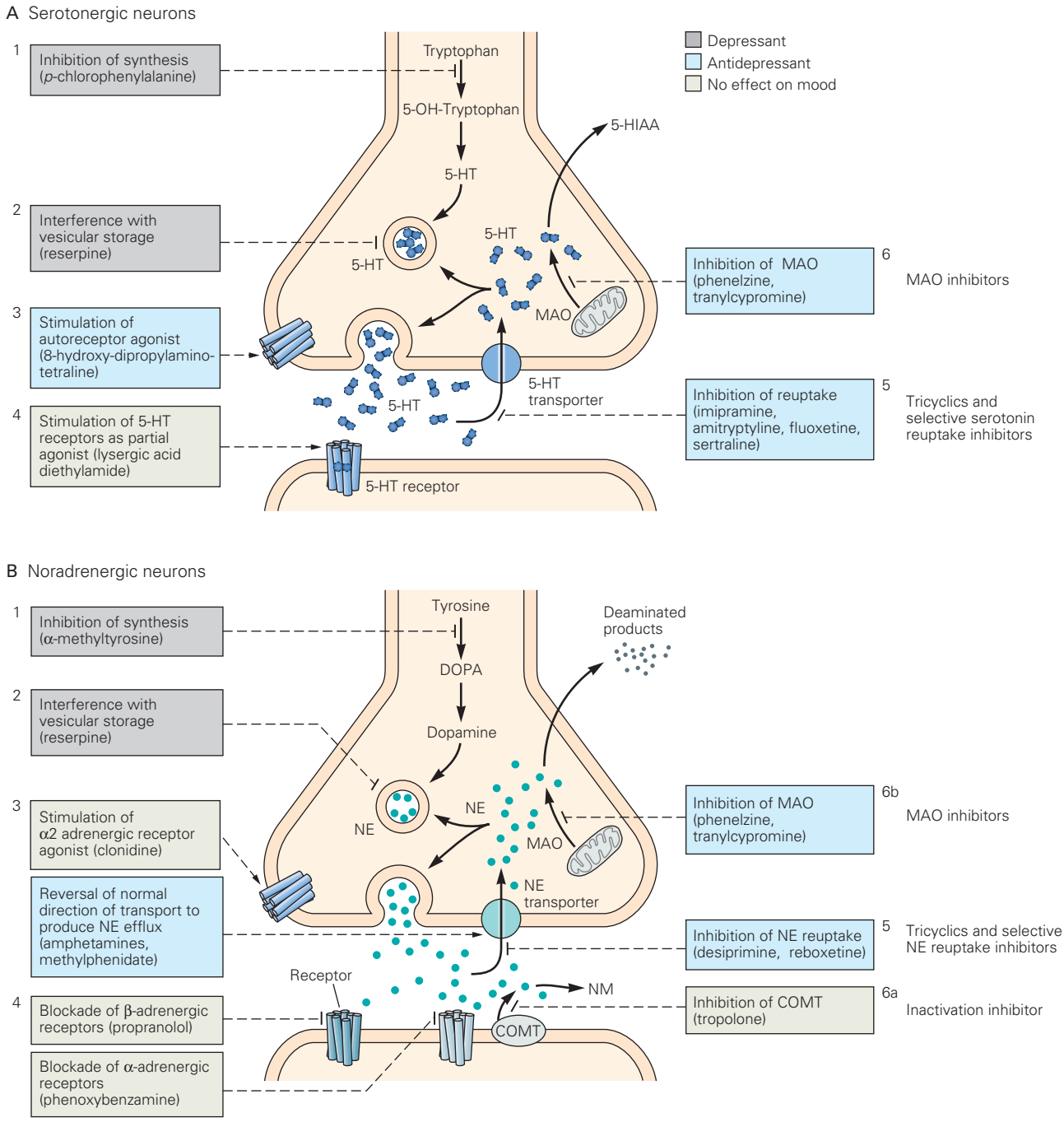
A Serotonergic neurons
Depressant
Antidepressant
No effect on mood
1
Inhibition of synthesis (p-chlorophenylalanine)
2
Interference with vesicular storage (reserpine)
3
Stimulation of autoreceptor agonist (8-hydroxy-dipropylamino-tetraline)
4
Stimulation of 5-HT receptors as partial agonist (lysergic acid diethylamide)
Tryptophan
5-OH-Tryptophan
5-HT
5-HIAA
5-HT
5-HT
MAO
5-HT transporter
5-HT
5-HT receptor
6
Inhibition of MAO (phenelzine, tranylcypromine)
MAO inhibitors
5
Inhibition of reuptake (imipramine, amitryptyline, fluoxetine, sertraline)
Tricyclics and selective serotonin reuptake inhibitors
B Noradrenergic neurons
1
Inhibition of synthesis (α-methyltyrosine)
2
Interference with vesicular storage (reserpine)
3
Stimulation of α2 adrenergic receptor agonist (clonidine)
Reversal of normal direction of transport to produce NE efflux (amphetamines, methylphenidate)
4
Blockade of β-adrenergic receptors (propranolol)
Blockade of α-adrenergic receptors (phenoxybenzamine)
Tyrosine
DOPA
Dopamine
Deaminated products
NE
NE
MAO
NE transporter
Receptor
NM
COMT
6b
Inhibition of MAO (phenelzine, tranylcypromine)
MAO inhibitors
5
Inhibition of NE reuptake (desiprimine, reboxetine)
Tricyclics and selective NE reuptake inhibitors
6a
Inhibition of COMT (tropolone)
Inactivation inhibitor

Figure 63–7 (Opposite) Actions of antidepressant drugs at serotonergic and noradrenergic synapses. The figure shows the pre- and postsynaptic sides of serotonergic and noradrenergic synapses. Serotonin and norepinephrine are synthesized from amino acid precursors by enzymatic cascades. The neurotransmitters are packaged in synaptic vesicles; free neurotransmitter within the cytoplasm is metabolized by monoamine oxidase, an enzyme that is associated with the abundant mitochondria found in presynaptic terminals. On release, serotonin and norepinephrine interact with several types of pre- and postsynaptic receptors (see Tables 63–3 and 63–4). Each neurotransmitter is cleared from the synapse by a specific transporter. The serotonin and norepinephrine transporters and monoamine oxidase are targets of antidepressant drugs.

A. Important sites of drug action at serotonergic synapses. Not all actions described are shown in the figure.

1. *Enzymatic Synthesis*. *p*-Chlorophenylalanine can inhibit the rate-limiting enzyme tryptophan hydroxylase, which initiates the cascade that converts tryptophan to 5-OH-tryptophan, the precursor of 5-hydroxytryptophan (**5-HT**, serotonin).

2. *Storage*. Reserpine and tetrabenazine interfere with the transport of serotonin and catecholamines into synaptic vesicles by blocking the vesicular monoamine transporter, $VMAT_2$. The cytoplasmic serotonin is degraded (see A. 6. below) and thus the neuron is depleted of neurotransmitter. Reserpine was used as an antihypertensive drug, but commonly caused depression as a side effect.

3. *Presynaptic Receptors*. Agonists at presynaptic receptors produce negative feedback on neurotransmitter synthesis or release. The agonist 8-hydroxy-diprolamino-tetraline (8-OH-DPAT) acts on 5-HT_{1A} receptors. The antimigraine triptan drugs (eg, sumatriptan) are agonists at 5-HT_{1D} receptors.

4. *Postsynaptic Receptors*. The hallucinogen lysergic acid diethylamide (LSD) is a partial agonist at 5-HT_{2A} receptors on the postsynaptic serotonergic neurons. Second-generation antipsychotic drugs, such as risperidone and olanzapine, are antagonists at 5-$HT2_A$ receptors in addition to their ability to block D_2 dopamine receptors. The antiemetic compound ondansetron is an antagonist at 5-HT_3 receptors, the only ligand-gated channel among the monoamine receptors. Its key site of action is in the medulla.

5. *Uptake*. The selective serotonin reuptake inhibitors, such as fluoxetine and sertraline, are selective blockers of the serotonin transporter. The tricyclic drugs have mixed actions; some, such as clomipramine, are relatively selective for the serotonin transporter. Uptake blockers increase synaptic concentrations of serotonin. Amphetamines enter monoamine neurons through the uptake transporter and interact with the vesicular transporter on synaptic vesicles to release neurotransmitter into the cytoplasm. The neurotransmitter is then pumped out of the neuron into the synapse through the uptake transporter acting in reverse.

6. *Degradation*. Phenelzine and tranylcypromine, both of which are effective for depression and panic disorder, block monoamine oxidase A and B (MAO_A and MAO_B). Moclobemide, effective against depression, is selective for MAO_A; selegiline, which has been used to treat Parkinson disease, is selective for MAO_B in low doses (5-HIAA, 5-hydroxyindoleacetic acid).

B. Important sites of drug action at noradrenergic synapses.

1. *Enzymatic synthesis*. The competitive inhibitor α-methyltyrosine blocks the reaction catalyzed by tyrosine hydroxylase that converts tyrosine to DOPA. A dithiocarbamate derivative, FLA 63 (not shown), blocks the reaction that converts DOPA to dopamine.

2. *Storage*. Reserpine and tetrabenazine interfere with the transport of norepinephrine, dopamine, and serotonin into synaptic vesicles by blocking the vesicular monoamine transporter $VMAT_2$. The cytoplasmic neurotransmitter is degraded (see A. 6. below) and thus the neuron is depleted of neurotransmitter.

3. *Presynaptic Receptors*. Agonists at presynaptic receptors produce negative feedback on neurotransmitter synthesis or release. Clonidine is an agonist at α_2 adrenergic receptors, inhibiting norepinephrine (**NE**) release. It has anxiolytic and sedative effects and is also used to treat attention deficit hyperactivity disorder. Yohimbine is an antagonist at α_2 adrenergic receptors; it induces anxiety.

4. *Postsynaptic Receptors*. Propranolol is an antagonist at β_2-adrenergic receptors that blocks many effects of the sympathetic nervous system. It is used to treat some forms of cardiovascular disease but is commonly used to block anxiety during performance situations. Phenoxybenzamine is an agonist at α-adrenergic receptors.

5. *Uptake*. Certain tricyclic antidepressants, such as desipramine, and newer norepinephrine selective reuptake inhibitors (**NRI**) such as reboxetine, selectively block the norepinephrine transporter, thus increasing synaptic norepinephrine. Amphetamines enter monoaminergic neurons through the uptake transporter and interact with the vesicular transporter on synaptic vesicles to release neurotransmitter into the cytoplasm. The neurotransmitter is then pumped out of the neuron into the synapse through the uptake transporter acting in reverse.

6. *Degradation*. At the postsynaptic neuron tropolone inhibits the enzyme catechol-*O*-methyltransferase (**COMT**), which inactivates norepinephrine (**6a**). Normetanephrine (**NM**) is formed by the action of COMT on norepinephrine. At the presynaptic neuron degradation by monoamine oxidase (**MAO**) is blocked by the monoamine oxidase inhibitors phenelzine and tranylcypromine (**6b**), as described in Figure 63–5.

has recently revealed that a single intravenous dose of ketamine, which blocks NMDA-type glutamate receptors, produces antidepressant effects within hours and that these effects persist for a week. Ketamine was developed as a dissociative anesthetic, a drug that distances a person from the experience of his body and produces other cognitive disturbances. However, in adults it may also produce psychotic-like symptoms and euphoria, and so is an abused street drug. A drug with such a profile of action is not likely to prove useful as an antidepressant, but it has led to promising new avenues of research focused on signaling initiated by NMDA receptors.

Overall, evidence for direct involvement of monoamines in pathogenesis remains scant. A large number of genetic studies attempting to link polymorphisms in genes that influence serotonergic function have remained inconclusive.

Psychotherapy Is Effective in the Treatment of Major Depression

Nonpharmacologic treatments are also effective in the treatment of major depression. Short-term symptom-focused psychotherapies have been developed for depression and tested in clinical trials. The best-studied psychotherapy used against depression is cognitive-behavioral therapy, which is effective in the treatment of mild and moderately severe major depression and in dysthymic disorder. Cognitive-behavioral therapy focuses on identifying and correcting distorted negative interpretations of events and automatic negative thinking that may initiate or perpetuate the depressed mood (see Box 61–1).

An important challenge is to understand what happens in the brain in response to such specialized forms of learning as cognitive-behavioral therapy. For example, such therapies may alter the activity of brain structures thought to mediate negative emotion, such as the amygdala and anterior cingulate cortex. The use of brain imaging techniques to demonstrate such changes may eventually help identify those patients who are particularly amenable to cognitive therapy and track their therapeutic progress, and my even be useful in training and therapy as a form of biofeedback.

Electroconvulsive Therapy Is Highly Effective Against Depression

Although it still conjures up negative images in the popular imagination, electroconvulsive therapy (ECT) administered with modern anesthesia is medically safe and remains the single most effective intervention for the acute treatment of serious major depression. It is also effective in both the depressed and manic phases of bipolar disorder. Electroconvulsive therapy is used when patients with major depression fail to respond to medication or when the patient is too debilitated to take medication.

Generally, six to eight treatments are given, most commonly on an outpatient basis, with unilateral lead placement. Bilateral placement can be used if unilateral is unsuccessful. Patients are anesthetized, and electrical stimulation is administered just to the degree that will produce electroencephalographic evidence of a generalized seizure. The major side effect is temporary memory impairment, with some retrograde amnesia. Amnesia is minimized by using unilateral lead placement and the lowest level of electrical stimulation needed. It is thought that electroconvulsive therapy increases the availability of biogenic amines in the brain, but its mechanism of action remains uncertain.

Motivated by the desire to improve on the therapeutic effects of ECT while diminishing its side effects, methods based on more focused forms of brain electrical stimulation are being explored. These include deep brain stimulation (DBS) using implanted electrodes and transcranial magnetic stimulation (TMS).

Bipolar Disorder Can Be Treated with Lithium and Several Drugs Initially Developed as Anticonvulsants

The discovery by John Cade in 1949 that lithium is effective in the treatment of mania initiated the modern era of psychopharmacology. In bipolar patients lithium not only treats acute episodes of mania but can also prevent recurrences of both mania and depression. It was thus the first "mood stabilizing" drug. Several drugs initially developed to treat epilepsy, such as valproic acid, were later shown to be effective in treating mania and in preventing recurrences of mania and depression.

The mechanism by which lithium stabilizes mood is not known. The two most promising ideas are based on lithium's ability to block enzymes involved in intracellular signaling pathways. Many neurotransmitter receptors indirectly activate phospholipase C through the G protein G_Q (eg, the α_1-norepinephrine, 5-HT_2 serotonin, and several muscarinic acetylcholine receptors). Phospholipase C hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to liberate two second messengers (Figure 63–8). PIP_2 is normally synthesized from free inositol. Central neurons cannot obtain free inositol from plasma because of the blood-brain barrier. They therefore must either recycle inositol, which requires the generation of inositol phosphates

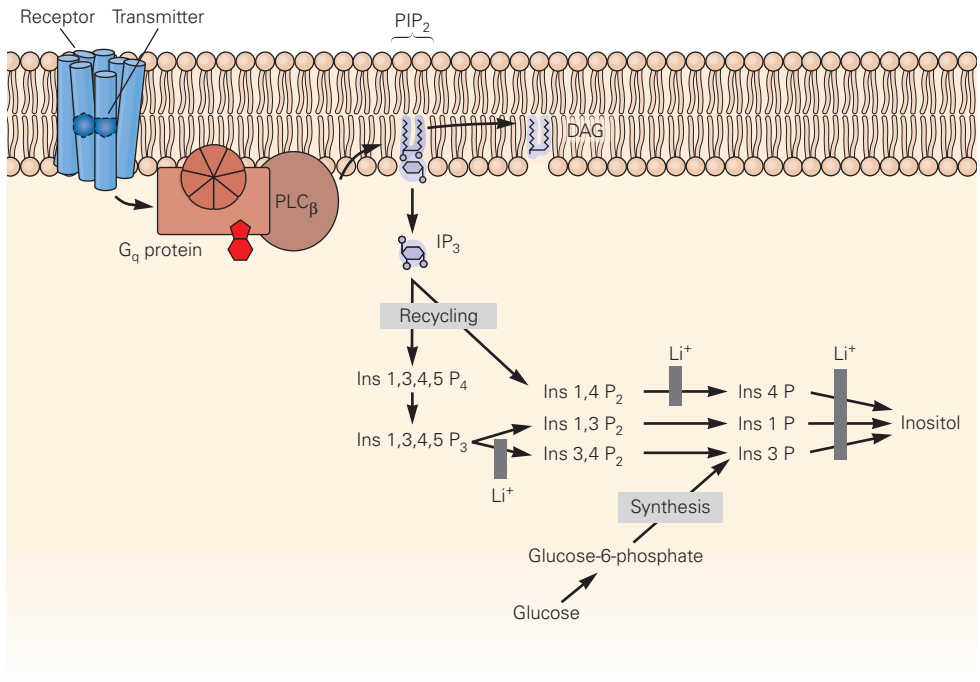

Figure 63–8 Lithium action on phosphatidylinositol pathways. A variety of neurotransmitter receptors are linked by the protein G_q (see Tables 63–3 and 63–4) to phospholipase C_β, which hydrolyzes phosphatidylinositol-4,5-biphosphate (**PIP_2**) to generate two second messengers, diacylglycerol (**DAG**) and inositol 1,4,5-triphosphate (**IP_3**). IP_3 releases Ca^{2+} from intracellular stores and subsequently is metabolized to forms that may not participate in neural signal transduction, including inositol 1,3,4,5-tetraphosphate (**Ins 1,3,4,5 P_4**). These are all metabolized to produce several inositol monophosphates, of which all are in turn metabolized by inositol monophosphate phosphatase, an enzyme that is inhibited by therapeutic concentrations of lithium (Li^+). De novo synthesis of inositol from glucose-6-phosphate also must pass through an inositol monophosphate intermediate. Thus in the presence of lithium the monophosphates derived from recycling of second messengers or from new synthesis cannot be dephosphorylated to yield free inositol. This should inhibit the ability of cells to regenerate PIP_2 and thus disrupt the second-messenger cascade. (Reproduced, with permission, from Nestler, Hyman, and Malenka 2009.)

by hydrolysis of phosphatidylinositols, or synthesize it from glucose-6-phosphate, a product of glycolysis.

Lithium inhibits several inositol phosphatases, including inositol-monophosphate-phosphatase, which is critical for the synthesis of the second messengers diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP_3) (Figure 63–8). As a result, lithium would appear to limit the ability of neurons to synthesize precursors of second messengers and therefore dampen the ability of neurons to fire at abnormally high rates. Alternatively, inositol depletion might alter gene expression that in turn would alter the response properties of critical neurons.

The second idea about how lithium stabilizes mood comes from the observation that lithium inhibits glycogen synthase kinase type 3 (GSK3), a critical enzyme in the Wnt signaling pathway (Figure 63–9). The Wnt signaling pathway plays important roles in brain development (see Chapter 53). How inhibition of this pathway might treat mania remains unknown.

Valproic acid is an anticonvulsant that also stabilizes mood. It appears to facilitate the actions of GABA (γ-aminobutyric acid), the key inhibitory neurotransmitter in the brain, possibly by increasing GABA release. The mechanisms by which anticonvulsants might treat bipolar disorder and the question of whether the mechanisms are shared with lithium remain important but unanswered.

Whatever the molecular mechanisms of lithium or the anticonvulsants, it seems likely that mood stabilizers dampen the dynamics of mood regulatory systems. Mood is regulated by the external environment as well as internal inputs, including the internal hormonal milieu, immune modulators, and circadian controls (eg, both the serotonergic and noradrenergic

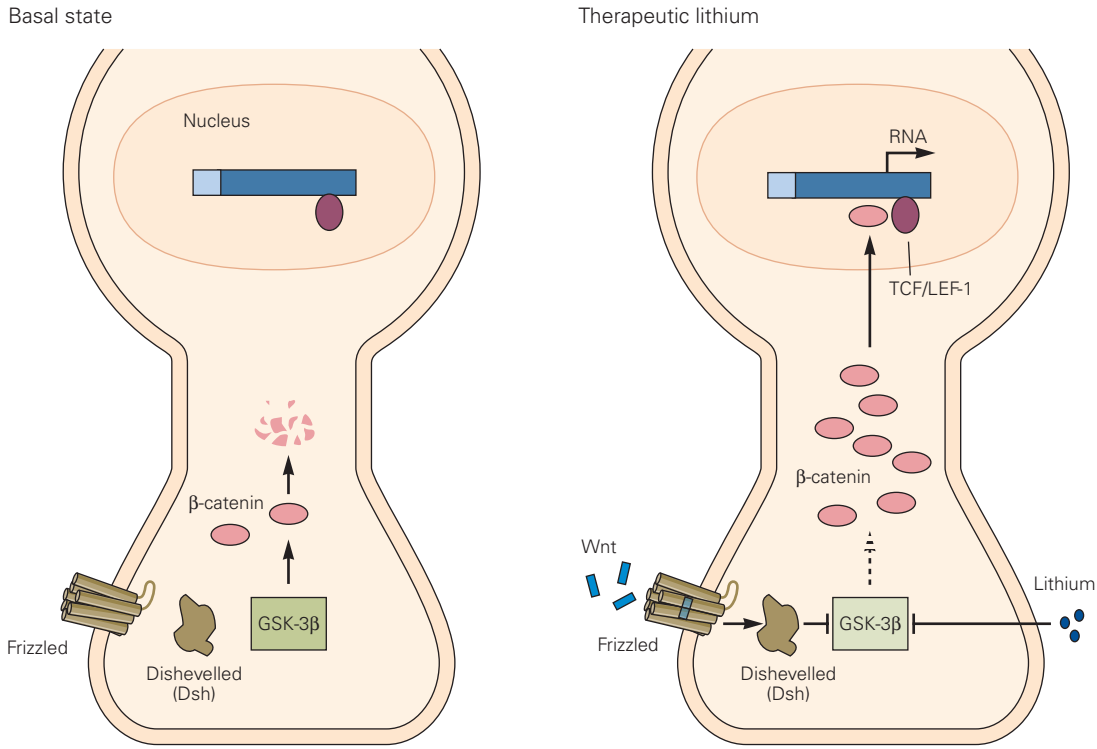

Figure 63–9 Lithium affects the Wnt signaling pathway. Wnt secretory proteins are involved in cell proliferation and differentiation. The Wnt protein was initially discovered as a critical molecule in *Drosophila* wing development but has been identified in the mammalian brain as well. Wnt binds receptors of the Frizzled family, initiating a signaling cascade to the nucleus that involves a cytosolic protein Dishevelled (**Dsh**) and glycogen synthase kinase 3β (**GSK-3β**). Phosphorylation by GSK-3β causes the degradation of another protein, β-catenin (left panel). GSK-3β is inhibited when Wnt binds Frizzled or when lithium is present in therapeutic concentrations, thus stabilizing β-catenin (right panel). When the level of β-catenin builds up, the protein translocates to the nucleus of the cell where it activates gene expression through a transcription complex TCF/LEF-1. Which genes might be induced by this pathway to stabilize mood is unknown. Interestingly, a Dsh knockout mouse exhibits abnormal social behavior and grooming. (Reproduced, with permission, from Nestler, Hyman, and Malenka 2009.)

systems show diurnal variations closely coupled with the sleep-wake cycle). The coupling of these systems is complex, involving dynamic interactions that are still poorly understood. Understanding these interactions is likely to give insight into the pathological cycle of bipolar disorder.

Anxiety Disorders Stem from Abnormal Regulation of Fear

Fear is a complex physiological, behavioral, cognitive, and, in humans, subjective response to a threatening stimulus. It evolved as an adaptive response to real threats and is usually transient. Anxiety is a longer-lasting response to danger signals that can arise either from immediate circumstances that signal well-defined danger or from vague indications of ill-defined events that are thought to have adverse consequences.

Anxiety can be highly adaptive; arousal, vigilance, and physical preparedness increase the likelihood of survival in dangerous situations. However, because many situations lack clear signs of safety, anxiety can persist. When anxiety persists beyond genuine risk, or when it produces a response out of proportion to the possible threat, the result can be distressing and disabling. Anxiety is the core symptom in several common psychiatric disorders. In the United States 28.5% of the population suffer from one or more anxiety disorders over the course of their lifetimes.

Anxiety disorders are distinguished from each other by the nature, intensity, and time course of symptoms, patterns of familial transmission, precipitating factors, the role of external cues in triggering episodes, and the constellation of associated symptoms. In some

situations anxiety is not produced by a single eliciting stimulus but by an accumulation of cues. The currently recognized anxiety disorders are panic disorder, post-traumatic stress disorder, generalized anxiety disorder, social anxiety disorder (also called social phobia), simple phobias, and obsessive-compulsive disorder.

Panic disorder. The cardinal symptom of panic disorder is the unexpected panic attack consisting of a discrete period of intense fear accompanied by somatic symptoms such as palpitations, shortness of breath, sweating, paresthesias, and dizziness, and by a powerful fear of losing control or of dying (Table 63–5). Panic disorder is diagnosed when panic attacks recur and give rise to anticipatory anxiety about future attacks. People with panic disorder might restrict their lives progressively to avoid situations or places in which attacks occur or from which they might not be able escape should they experience an attack. It is common for patients to avoid crowds, bridges, and elevators; some individuals eventually stop leaving home altogether. A generalized phobic avoidance is called *agoraphobia*.

Post-traumatic stress disorder. Post-traumatic stress disorder (PTSD) follows an experience of severe danger or injury. First recognized in soldiers during World War I after combat trauma, it also occurs after civilian traumas such as violent assaults or serious accidents. It is characterized by emotional numbness to ordinary stimuli, punctuated by painful reliving of the traumatic episode, often initiated by sounds, images, or odors that trigger highly charged memories of the circumstances in which the trauma occurred. For example, a Vietnam War veteran with PTSD might experience intense symptoms after hearing a traffic helicopter pass overhead (recalling the heavy use of assault helicopters in that war). It is also characterized by disturbed sleep that can include nightmares, and by hyperarousal, such as an exaggerated startle response.

Generalized anxiety disorder. This disorder is characterized by chronic (months-long) worry and vigilance that is not warranted by circumstances. This worry is accompanied by physiological disturbances such as heightened sympathetic nervous system arousal (evidenced by an increase in heart rate) and by motor tension.

Social anxiety disorder. This disorder is characterized by a persistent fear of social situations or performance situations that expose a person to the scrutiny of others. The patient 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 special circumstances, such as public speaking. Generalized social anxiety, as its name implies, involves adverse responses to most social situations and can therefore prove quite disabling.

Simple phobias consist of intense, excessive fear of specific stimuli, such as snakes, spiders, or height.

Obsessive-compulsive disorder. Obsessive-compulsive disorder (OCD) is characterized by obsessions (intrusive, unwanted thoughts) and compulsions (performance of highly ritualized behaviors intended to neutralize the negative thoughts and emotions resulting from the obsessions). The person experiences the obsessions as foreign and unwanted. Attempts to resist the urge to perform the compulsive acts result in high levels of anxiety. Typical symptom patterns are repetitive hand washing to neutralize fears of contamination (sometimes hours a day to the point of skin damage), or repeatedly checking the front door to see that it is locked.

Although current classifications of psychiatric disorders, including *DSM-IV*, place OCD among the anxiety disorders, family studies and imaging studies suggest that the disorder may share risk factors and dysfunction of striatal circuits with Tourette disorder, which is characterized by motor tics (involuntary, rapid movements) as well as vocal tics—grunts, noises, obscenities—and is often accompanied by obsessive-compulsive symptoms. Additional evidence for primary problems in striatal circuits, rather than the amygdala circuits implicated in other anxiety disorders, comes from the study of Sydenham chorea,

Table 63–5 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:
Palpitations, pounding heart, or accelerated heart rate
Sweating
Trembling or shaking
Sensations of shortness of breath or smothering
Feeling of choking
Chest pain or discomfort
Nausea or abdominal distress
Feeling dizzy, unsteady, lightheaded, or faint
Derealization (feelings or unreality) or depersonalization (being detached from oneself)
Fear of losing control or going crazy
Fear of dying
Paresthesias (numbness or tingling sensations)
Chills or hot flushes

a movement disorder that can result from acute rheumatic fever. Interestingly, many patients with Sydenham chorea experience transient OCD-like symptoms. Sydenham chorea results from antibodies developed in response to a streptococcal infection, and the antibodies have been shown to bind to neurons in the striatum. OCD can be treated with high doses of selective serotonin reuptake inhibitor and by psychotherapy aimed at stopping intrusive thoughts and compulsive rituals.

Anxiety Disorders Have a Genetic Component

Panic disorder, generalized anxiety disorder, phobias, and OCD all run in families. First-degree relatives of individuals with panic disorder have a significantly greater risk of panic disorder than the general population or the first-degree relatives of unaffected control subjects.

Twin studies have concluded that panic disorder, generalized anxiety disorder, and probably phobias are explained to a large extent by genes. Twin studies also suggest overlapping genetic risk factors for depression and generalized anxiety disorder, which helps explain the observation that these two disorders often occur together.

In post-traumatic stress disorder genes appear to act in two important ways. They influence (1) the risk of developing the disorder after exposure to traumatic events and (2) the likelihood of individuals exposing themselves to dangerous situations.

Animal Models of Fear May Shed Light on Human Anxiety Disorders

Because many responses to fearful stimuli are conserved across mammalian species, animal models are potentially relevant to human disorders. In addition, because stimuli that elicit fear and anxiety can be readily produced in the laboratory, animal models are amenable to study. Studies using animal models have focused on two general classes of fear: innate fear and learned fear.

Studies of innate or instinctual fear exploit the natural tendencies of rats and mice to avoid open spaces or other situations that expose them to predators (Figure 63–10). Studies of learned or conditioned fear exploit the ability of rodents and other animals to form powerful associations between previously neutral cues and temporally linked danger. As described in Chapter 48, studies using these animal models have led to the outline of an amygdala-based fear circuitry that mediates defensive behaviors and appropriate physiologic responses to danger. They have been useful in designing noninvasive studies of human subjects with anxiety disorders, and as screens for anxiety-reducing drugs and genetic mutations that influence fear.

Our growing understanding of fear circuitry has generated testable hypotheses about the pathophysiology of

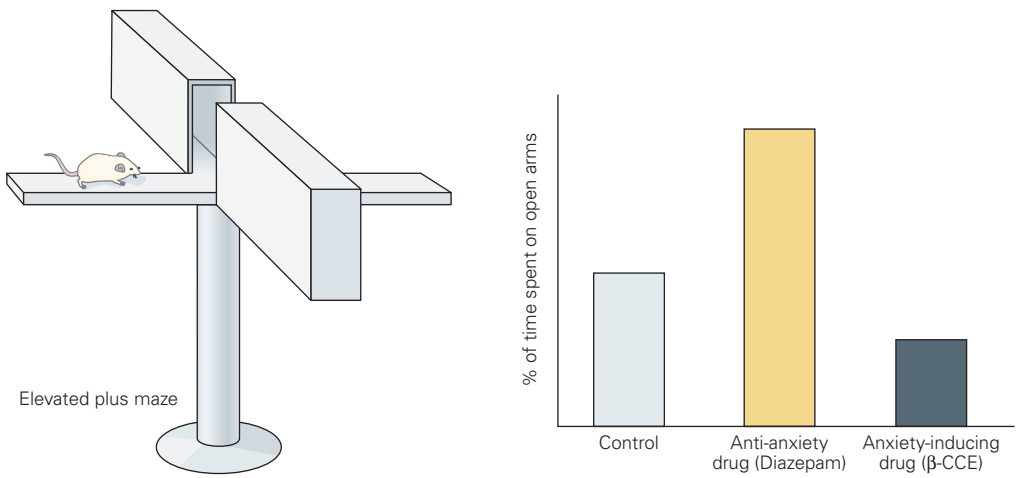

Figure 63–10 The effects of anxiety-reducing drugs can be tested on rodents in the elevated plus maze. The apparatus has two intersecting arms, one enclosed and the other open. A rat or mouse is placed at the intersection and the time spent on the open or enclosed arms is measured. Rodents normally prefer the closed arm. Rodents given benzodiazepine drugs, such as diazepam, which reduce anxiety in humans, spend more time in the open arm. Rodents given the benzodiazepine inverse agonist β-carboline (β-CCE), which strongly induces anxiety in humans, spend less time in the open arm. (Reproduced, with permission, from Nestler, Hyman, and Malenka 2009.)

human anxiety disorders such as post-traumatic stress disorder. For example, fear conditioning occurs normally in humans and is usually adaptive. By learning cues that signify danger and developing efficient responses, an individual minimizes future risk of harm. The central abnormality in post-traumatic stress disorder appears to be fear conditioning that is excessive, such that later minor cues are able to elicit fear responses. This dysregulated fear response alters other cognitive, emotional, and physiological responses. By mechanisms that are not yet well understood, it may alter basal levels of arousal, leading to exaggerated startle responses and disordered sleep. Other aspects of post-traumatic stress disorder, such as emotional numbing, are more difficult to model in experimental animals.

The unexpected panic attack—the hallmark of panic disorder—may represent a "false alarm" in which the fear circuitry is activated in the absence of a threat. Whether such abnormal activation originates from the fear circuitry itself or elsewhere in the nervous system is not known. Panic attacks can be produced in susceptible people by increasing partial pressure of carbon dioxide (PCO_2) in their blood or administering caffeine or drugs, which increase sympathetic outflow. Although these observations suggest a low threshold for activating the fear circuitry in persons with panic disorder, we do not yet understand the neurophysiologic mechanisms that trigger spontaneous panic attacks.

Panic attacks can be a source of fear conditioning. Initially, panic attacks are usually spontaneous, with no obvious relationship to the immediate context or environmental stimuli. However, environmental cues experienced in conjunction with a panic attack can become fear-associated stimuli. Later, these cues can trigger severe anticipatory anxiety or even a full panic attack.

With simple phobias and social anxiety the fear circuitry may be activated by cues that ordinarily signal very limited, if any, danger, such as risk of embarrassment. The experience can lead to avoidance of the cues. A person with a phobia of air travel might limit travel to surface transportation, and a person with stage fright might alter career plans to avoid public speaking.

Neuro-imaging Implicates Amygdala-Based Circuits in Human Fear and Anxiety

The understanding of the neural circuitry underlying fear and anxiety in animal models has guided neuroimaging studies of humans. In healthy subjects the amygdala is activated in response to stimuli that reliably induce fear, such as faces portraying fear, as well as during fear conditioning.

In a functional magnetic resonance imaging (fMRI) study of normal volunteers the presentation of a face portraying fear activated the dorsal subregion of the amygdala; this region contains what is thought to be the amygdala's main output nucleus, the central nucleus. When the same faces were shown only briefly to these subjects, followed by a neutral face (referred to as backward masking), the subjects did not report awareness of having seen the fearful face. Yet they exhibited physiological signs of fear (activation of the sympathetic nervous system). This test paradigm activates the basolateral subregion of the amygdala (which contains inputs from the thalamus and cerebral cortex) in healthy subjects similar to that of subjects with anxiety disorders (Figure 63–11).

Functional neuroimaging has also revealed heightened activity in the amygdala in specific anxiety disorders, including social anxiety disorder and post-traumatic stress disorder. In individuals with social anxiety disorder the increase in activity is induced by images of fearful faces; in individuals with post-traumatic stress disorder it is induced by narratives that are reminiscent of their trauma.

Structural imaging has also been used to study anxiety disorders. The most often replicated structural finding is diminished hippocampal volume in individuals with depression or post-traumatic stress disorder. Until longitudinal studies are performed, it is not clear whether a small hippocampus is a risk factor for post-traumatic stress disorder or a result of the disorder.

Anxiety Disorders Can Be Treated Effectively with Medications and Psychotherapy

Cognitive-behavioral therapies designed for specific anxiety disorders have proved as effective as medication in the treatment of anxiety disorders. For example, a person with cue-elicited anxiety, whether a simple phobia, phobic avoidance resulting from panic disorder, or social anxiety disorder, is coached to confront the phobic stimulus with adequate support and a new cognitive schema for coping with the fear. For many patients a combination of medication and cognitive-behavioral therapy may prove necessary.

Among the medications used for various anxiety disorders, drugs that were initially developed as antidepressants have proven highly efficacious and are the drugs of choice. The selective serotonin reuptake inhibitors are most widely used because they are easily tolerated. Simple phobias are best treated with cognitive-behavioral therapy rather than medication. The response of obsessive-compulsive disorder to treatment differs from those anxiety disorders in which amygdala-based

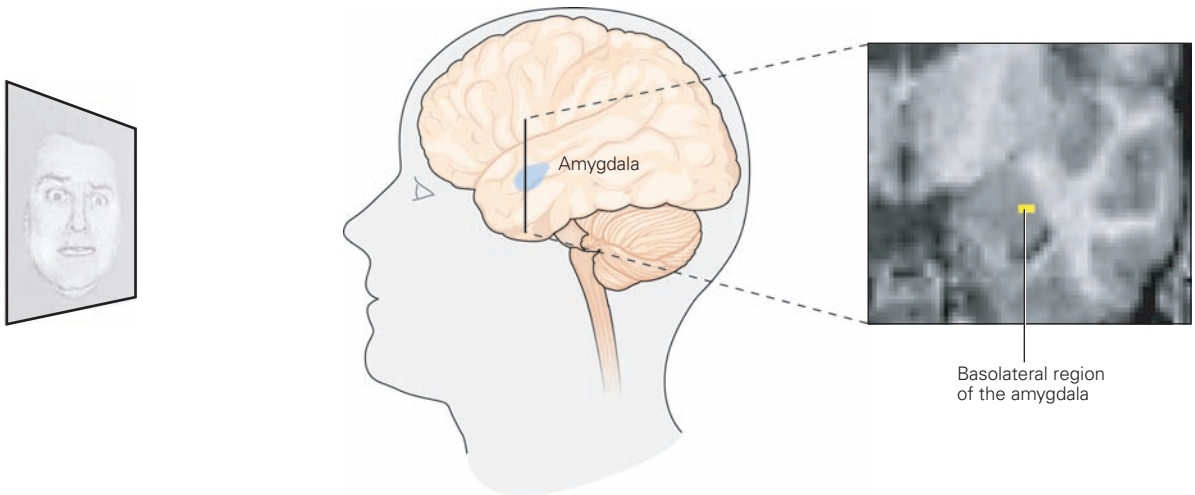

Figure 63–11 Amygdala activation in response to a masked presentation of a fearful stimulus. A human subject observes projected images while being scanned by magnetic resonance imaging. When a fearful face is presented for a very brief time followed by presentation of a neutral face (a protocol called *backward masking*), the subject is not consciously aware of the fearful face. Under these conditions the basolateral region of the amygdala predicts individual differences in trait anxiety in healthy subjects similar to those found in patients with anxiety disorders. (Reproduced, with permission, from Etkin et al. 2004.)

fear circuitry is thought to be the primary abnormality. Obsessive-compulsive disorder responds only to serotonin selective drugs at higher doses. Medications are generally combined with cognitive-behavioral therapy specially designed to inhibit compulsive behaviors.

Another class of drugs, the benzodiazepines, are occasionally used for generalized anxiety disorder, whereas higher doses are used for panic disorder. However, existing benzodiazepines can cause sedation; indeed, they are also used as hypnotics, and can degrade cognitive function. Moreover, benzodiazepines can cause dependence (as evidenced by worsened, so-called rebound anxiety) and insomnia when drugs are discontinued. In some individuals they can produce addiction (see Chapter 49). An advantage of the benzodiazepines is they react rapidly following a single dose, in contrast to the antidepressants, which can take weeks to become effective. Overall, they are second-line treatments to the selective serotonin reuptake inhibitors and other antidepressants, often used temporarily until the response to antidepressants takes effect.

The benzodiazepines produce their therapeutic effect by enhancing the inhibitory action of GABA at $GABA_A$ receptors. This receptor is ionotropic and selective for Cl^-. It is a pentamer, organized like barrel staves around an aqueous pore (Figure 63–12). Allosteric binding of benzodiazepine modifies the receptor complex, increasing the affinity of the GABA binding site for GABA. As a result, GABA-activated Cl^- channels open more frequently, enhancing the hyperpolarizing effect of GABA on the neuron. The sedative barbiturate drugs also bind the $GABA_A$ receptor complex, but at a site near the Cl^- channel. Barbiturates increase not only the affinity of the receptor for GABA but also channel open time, creating a greater risk of excessive central nervous system depression than is seen with benzodiazepines.

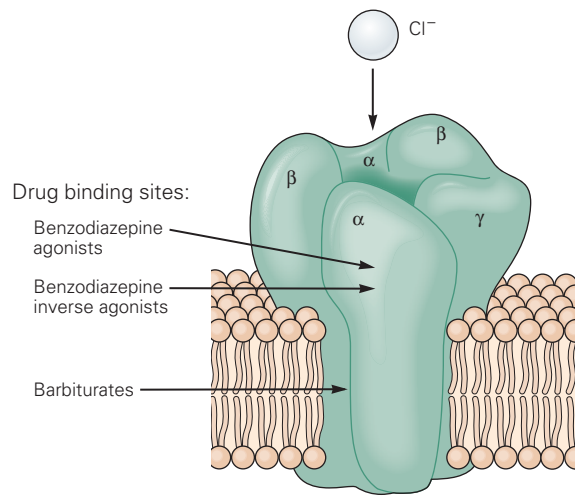

Figure 63–12 The $GABA_A$ receptor complex. The $GABA_A$ (γ-aminobutyric acid A) receptor is a pentamer arranged to form a Cl^- channel. In addition to the neurotransmitter GABA, the receptor binds several important drugs, including benzodiazepines and barbiturates, at physically separate sites.

An Overall View

Mood and anxiety disorders have long been misunderstood, even to the point that affected individuals can become objects of stigma. Because mood and anxiety disorders have a far greater impact on disability than on mortality (despite the risk of suicide), these disorders have too often been given low priority by healthcare systems.

These unfortunate circumstances are beginning to change. Modern epidemiological and economic research has documented the enormous burden created by these disorders, which tend to begin early in life and to interfere with learning in young people and the ability to work in adults. Increased scientific understanding has also made a difference.

Although there is still a long way to go before we understand fully the neural basis of these disorders or the genetic, developmental, and environmental risk factors that give rise to them, there is little doubt that mood and anxiety disorders are real disorders of the brain. For example, compelling hypotheses concerning the neural circuits underlying anxiety disorders have been put forth and are being tested, and neuroimaging has provided important leads in the study of mood disorders.

The existing treatments for chronic mood and anxiety disorders are generally not curative. However, existing medications and cognitive-behavioral therapies can markedly improve symptoms, even to the point of remission for many individuals. The study of mood and anxiety disorders is a challenging frontier for neural science, but a challenge with very significant rewards for human health.

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Selected Readings

American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. Washington, DC: American Psychiatric Association.

Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. 2002. Depression: perspectives from affective neuroscience. Annu Rev Psychol 53:545–574.

Delgado MR, Nearling KI, LeDoux JE, Phelps EA. 2008. Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. Neuron 59:829–838.

Gordon JA, Hen R. 2004. Genetic approaches to the study of anxiety. Annu Rev Neurosci 27:193–222.

Yehuda R. 2002. Post-traumatic stress disorder. N Engl J Med 346:108–114.

References

Barlow DH, Gorman JM, Shear MK, Woods SW. 2000. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. JAMA 283:2529–2536.

Beaulieu JM, Gainetdinov RR, Caron MG. 2009. Akt/GSK3 signaling in the action of psychotropic drugs. Annu Rev Pharmacol Toxicol 49:327–347.

Berndt ER, Koran LM, Finkelstein SN, Gelenberg AJ, Kornstein SG, Miller IM, Thase ME, Trapp GA, Keller MB. 2000. Lost human capital from early-onset chronic depression. Am J Psych 157:940–947.

Bouton ME, Mineka S, Barlow DH. 2001. A modern learning theory perspective on the etiology of panic disorder. Psychol Rev 108:4–32.

David DJ, Samuels BA, Rainer Q, Wang JW, Marsteller D, Mendez I, Drew M, et al. 2009. Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression. Neuron 62:479–493.

Davidson RJ, Putnam KM, Larson CL. 2000. Dysfunction in the neural circuitry of emotion regulation–a possible prelude to violence. Science 289:591–594.

Dohrenwend BR, Turner JB, Turse NA, Adams BG, Koenen KC, Marshall R. 2006. The psychological risks of Vietnam for U.S. veterans: a revisit with new data and methods. Science 313:979–982.

Etkin A, Klemenhagen KC, Dudman JT, Rogan MT, Hen R, Kandel ER, Hirsch J. 2004. Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. Neuron 44:1043–1055.

Frank E, Thase ME. 1999. Natural history and preventative treatment of recurrent mood disorders. Annu Rev Med 50:453–468.

Frodl TS, Koutsouleris N, Bottlender R, Forn C, Jager M, Scupin I, Reiser M, Holler HJ, Meisenzahl EM. 2008. Depression-related variation in brain morphology over 3 years. Effects of stress? Arch Gen Psychiatry 65:1156–1165.

Gross C, Hen R. 2004. The developmental origins of anxiety. Nat Rev Neurosci 5:545–552.

Heimer L. 1995. *The Human Brain and Spinal Cord,* 2nd ed. New York, Berlin: Springer-Verlag.

Hu H, Real E, Takamiya K, Kang MG, LeDoux J, Huganir RL, Malinow R. 2007. Emotion enhances learning via norepinephrine regulation of AMPA-receptor trafficking. Cell 131:160–173.

Hyman SE, Nestler EJ. 1996. Initiation and adaptation: a paradigm for understanding psychotropic drug action. Am J Psychiatry 153:151–162.

International Schizophrenia Consortium: Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P, et al. 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460:748–762.

Kendler KS, Aggen SH, Knudsen GP, Røysamb E, Neale MC, Reichborn-Kjennerud T. 2011. The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II disorders. Am J Psychiatry168:29–39.

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Wlters EE, Wang PS. 2003. The epidemiology of major depressive disorder: results from the National Comorbidity Survey replication (NCS-R). JAMA 289:3095–3105.

Krishnan V, Nestler EJ. 2008.The molecular neurobiology of depression. Nature 455:894–902.

Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS. 2010. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329:959–964.

Low K, Crestani F, Keist R, Benke D, Brunig I, Benson JA, Fritschy JM, et al. 2000. Molecular and neuronal substrate for the selective attenuation of anxiety. Science 6:131–134.

Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH. 2005. Deep brain stimulation for treatment-resistant depression. Neuron 45:651–660.

Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, Silva JA, McGinnis S, Glass TG, Martin CC, Fox PT. 1997. Cingulate function in depression: a potential predictor of treatment response. Neuroreport 8:1057–1061.

Mineka S, Watson D, Clark LA. 1998. Comorbidity of anxiety and unipolar mood disorders. Annu Rev Psych 49: 377–412.

Nestler EJ, Hyman SE, Malenka RJ. 2009. *Molecular Neuropharmacology. A Foundation for Clinical Neuroscience*, 2nd ed. New York: McGraw-Hill.

Nock MK. 2010. Self-injury. Annu Rev Clin Psychol 6:339–363.

Pizzagalli D, Pascual-Marqui RD, Nitschke JB, Oakes TR, Larson CL, Abercrombie HC, Schaefer SM, Koger JV, Benca RM, Davidson RJ. 2001. Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. Am J Psychiatry 158:405–415.

Sheline YI, Sanghavi M, Mintun MA, Gado MH. 1999. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci 19:5034–5043.

Shin LM, Wright CI, Cannistraro PA, Weddig MM, McMullin K, Martis, B, Macklin ML, et al. 2005. A functional magnetic resonance imaging study of amygdala and medial prefrontal cortex responses to overtly presented fearful faces in posttraumatic stress disorder. Arch Gen Psychiatry 62:273–281.

Wray NR, Pergadia ML, Blackwood DH, Penninx BW, Gordon SD, Nyholt DR, Ripke S, et al. 2010. Genome-wide association study of major depressive disorder: new results, meta-analysis, and lessons learned. Mol Psychiatry 2 November 2010; doi: 10.1038/mp.2010.109.

Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK. 2006. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 63:856–864.