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

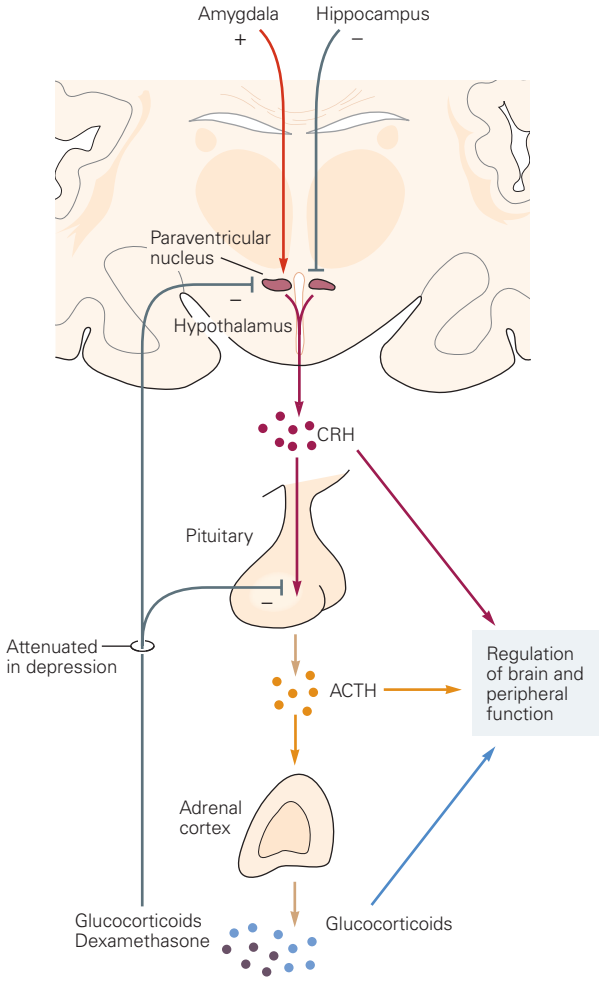


Figure 61–1 The hypothalamic-pituitary-adrenal axis. Neurons in the paraventricular nucleus of the hypothalamus synthesize and release corticotropin-releasing hormone (**CRH**), the key regulatory peptide in the hormonal cascade activated by stress. The CRH neurons have a circadian pattern of secretion, 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.)

stress-induced syndromes in these animal models has been strengthened by the observation that many antidepressant drugs reverse stress-induced changes in physiology or behavior in these animals. However, the degree to which animals subjected to diverse chronic stressors actually model the disease mechanisms underlying depression in human beings remains unknown. Concern about overreliance on stress-based and other rodent models is indicated by the failure to identify new antidepressant mechanisms despite more than 50 years of trying. Drug screens using such models have only identified molecules with actions similar to prototype antidepressant drugs that were first identified by their unexpected psychotropic effects on humans.

Dysfunctions of Human Brain Structures and Circuits Involved in Mood and Anxiety Disorders Can Be Identified by Neuroimaging

Investigation of human brain regions and the neural circuitry involved in mood and anxiety disorders has relied on noninvasive structural and functional neuroimaging, neurophysiologic testing, and postmortem analyses. More recently, information is being gleaned from neuroimaging of patients being treated with deep brain stimulation.

Identification of Abnormally Functioning Neural Circuits Helps Explain Symptoms and May Suggest Treatments

Functional neuroimaging and electrophysiological studies are being pursued in order to elucidate abnormalities in circuit activity and in patterns of intrinsic connectivity in mood and anxiety disorders. Given the heterogeneity of major depression, bipolar disorder, and anxiety disorders defined by current diagnostic methods, it has been challenging to identify robust and replicable abnormalities. In addition, the use of diverse cognitive and emotional tasks to experimentally probe mood and anxiety disorders has limited researchers' ability to replicate and confirm findings. Overcoming the resulting uncertainties will require larger numbers of subjects, application of data standards that permit meta-analyses, and increasingly, methods such as use of the PRSs to stratify subjects.

Despite current limitations, fMRI and electrophysiological studies of mood and anxiety disorders have begun to provide initial empirical leads about circuit abnormalities in mood and anxiety disorders. Resting-state fMRI studies comparing subjects with major depression and healthy control subjects suggest differences in patterns of intrinsic connectivity, specifically within neural circuits that regulate "top down" control of cognition and emotion—the "cognitive control network"—and in circuits that process significant emotional and motivational stimuli—"the salience network" (Figure 61–2). Despite the need for replication, these findings are noteworthy because they are consistent with results from task-based imaging studies of humans (eg, studies of fear conditioning) and animal studies that investigate responses to aversive stimuli.

In healthy human subjects, regions of the amygdala are activated by threatening stimuli and during fear conditioning, such as pairing a previously neutral tone with a mild shock. Beginning with the work of Charles Darwin, human faces expressing fear have been recognized to elicit anxiety responses across diverse human cultures, presumably as a mechanism to communicate the presence of danger among members of a group.

The effects of fearful and other emotion-expressing faces on measurements of autonomic activity and brain activity measured by fMRI or by electroencephalography have been studied in subjects with anxiety disorders or with major depression. In one such paradigm, fearful faces are shown very briefly (33 ms) while the subject is in an MRI scanner. This presentation is followed by a neutral face (referred to as backward masking). Under such circumstances, subjects report that they have no awareness of having seen the fearful face. Yet they exhibit an altered galvanic skin response, a measure of sympathetic activation, as well as activation of the basal amygdala, the amygdala region that processes sensory inputs and that responds selectively to threat. Several functional neuroimaging studies of individuals with PTSD, other anxiety disorders, and major depression have demonstrated heightened activity in the amygdala, activation even to innocuous stimuli, and persistence of amygdala activity in contrast to normal patterns of adaptation (Figure 61–3).

Functional neuroimaging studies of anxiety disorders and major depression have also found decreased activity in prefrontal cortical regions that are interconnected with the basal amygdala. Studies of animals with prefrontal cortical lesions demonstrate that projections from the prefrontal cortex to the basal amygdala are necessary for cognitive control over aversive information. In individuals suffering from anxiety disorders or major depression, reduced activation of the prefrontal cortex by aversive stimuli is consistent with cognitive testing that demonstrates decreased cognitive control and might contribute to excessive and persistent anxiety and other negative emotions.

Electrophysiological and functional neuroimaging studies of both major depression and bipolar disorder

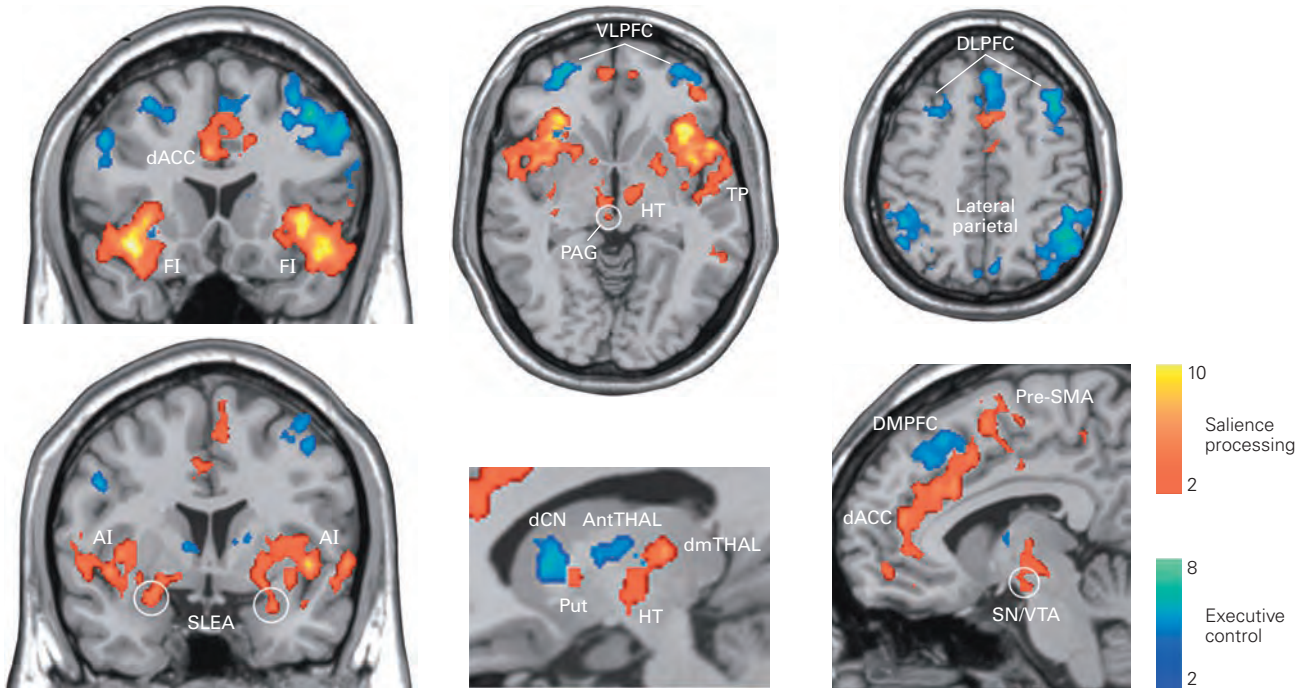


Figure 61–2 **Mood disorders involve independent neural networks associated with processing of emotional salience and cognitive control.** Statistical analysis (independent component analysis) applied to resting-state functional magnetic resonance imaging data identifies separable networks that compute emotional salience (**red-orange**) and regulate cognitive control/executive function (**blue**). The emotional salience network links dorsal anterior cingulate cortex (**dACC**) and frontoinsular cortex (**FI**) with subcortical structures involved in emotion. The cognitive control network links the dorsolateral prefrontal (**DLPFC**) and parietal cortices and several subcortical structures. The brain regions shown to be networked in this study have been implicated in major depression by multiple independent studies. (Abbreviations: **AI**, anterior insula; **antTHAL**, anterior thalamus; **dCN**, dorsal caudate nucleus; **DMPFC**, dorsomedial prefrontal cortex; **dmTHAL**, dorsomedial thalamus; **HT**, hypothalamus; **PAG**, periaqueductal gray matter; **Pre-SMA**, pre–supplementary motor area; **Put**, putamen; **SLEA**, sublenticular extended amygdala; **SN/VTA**, substantia nigra and ventral tegmental area of the midbrain; **TP**, temporal pole; **VLPFC**, ventrolateral prefrontal cortex.) (Reproduced, with permission, from Seeley et al. 2007. Copyright © 2007 Society for Neuroscience.)

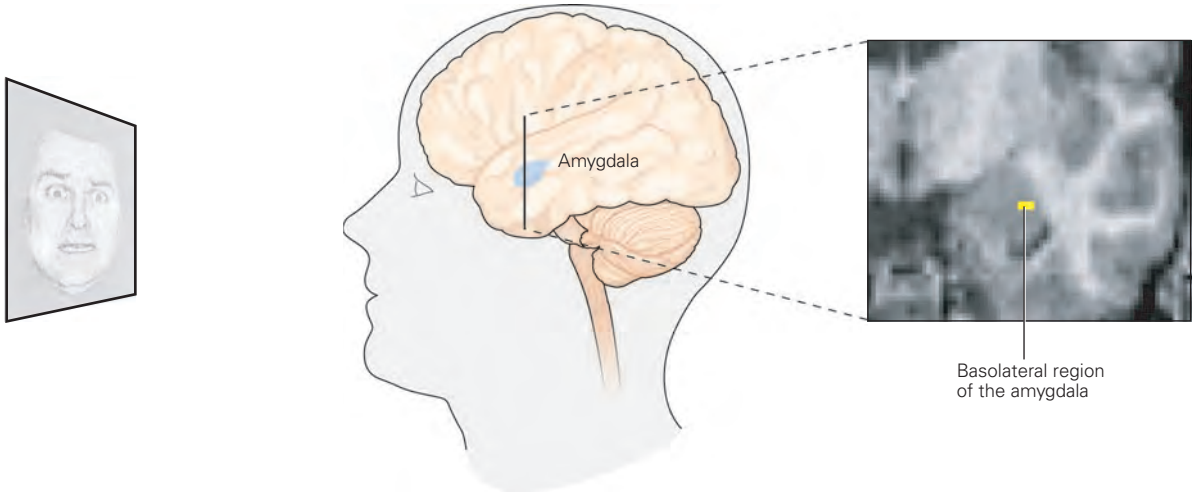


Figure 61–3 **Amygdala activation in response to a masked presentation of a fearful stimulus.** A human subject observes projected images while being scanned by magnetic resonance imaging. When a fearful face is presented for a very brief time followed by presentation of a neutral face, a protocol called backward masking, the subject is not consciously aware of the fearful face. Under these conditions, the basolateral region of the amygdala is more strongly activated in individuals with anxiety disorder than in normal individuals. (Reproduced, with permission, from Etkin et al. 2004.)

have shown abnormal functioning of the rostral and ventral subdivisions of the anterior cingulate cortex (ACC), a region of prefrontal cortex that participates in the emotional salience network. The rostral and ventral ACC have extensive connections with the hippocampus, amygdala, orbital prefrontal cortex, anterior insula, and nucleus accumbens and are involved in the integration of emotion, cognition, and autonomic nervous system function. The caudal subdivision of the ACC is involved in cognitive processes involved in control of behavior; it has connections with dorsal regions of the prefrontal cortex, secondary motor cortex, and posterior cingulate cortex.

Although abnormal function in both subdivisions of the ACC has been observed in depressive episodes, the most consistent abnormality observed in major depression and in the depressed phase of bipolar disorder is increased activity in the rostral and ventral subdivisions, especially in the subgenual region ventral to the genu (or "knee") of the corpus callosum. In a study using positron emission tomography, effective treatment of major depression with selective serotonin reuptake inhibitor antidepressants was correlated with decreased activity in the rostral ACC, whereas self-induced sadness in healthy subjects increased activity (Figure 61–4). Based on such studies, the rostral anterior (subgenual) cingulate cortex has been used as a target for electrode placement in deep brain stimulation for treatment-resistant major depression, which is operationally defined as depressive illness that has been unresponsive to antidepressant medication and psychotherapy.

Functional abnormalities of brain reward circuitry may also play a role in the symptoms of mood disorders. The reward circuitry comprises the dopaminergic projections from the ventral tegmental area of the midbrain to forebrain targets, including the nucleus accumbens, habenula, prefrontal cortex, hippocampus, and amygdala (Chapter 43). Under normal conditions, these pathways are involved in the valuation of rewards (eg, palatable food, sexual activity, and social interactions) and in motivating the necessary behavior to obtain them. Reward processing appears to be abnormal in depression, based on such symptoms as decreased interest in previously pleasurable activities, decreased motivation, and, when depression is severe, the inability to experience pleasure (anhedonia). Although less well studied, reward processing is also likely abnormal in mania, which is characterized by excessive engagement in goal-directed behaviors, even when they are maladaptive, such as uncontrolled spending, dangerous drug use, and promiscuous sexual activity.

In a recent analysis of resting-state fMRI, data showed that patients with major depression could be stratified based on connectivity patterns that correlated with their degree of anhedonia and anxiety. However, although modulation of the reward circuitry has been considered as a possible treatment for major depression, it has proven difficult in practice. For example, drugs known to activate this circuitry by

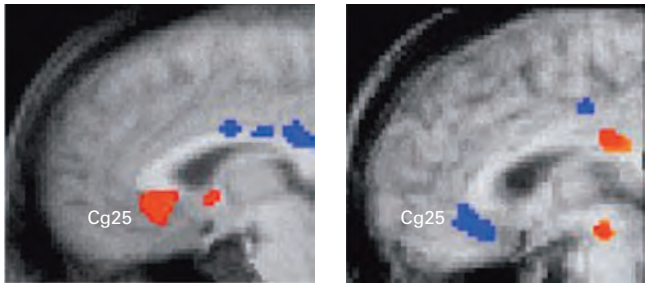


Figure 61–4 Activity in the rostral anterior (subgenual) cingulate cortex is increased by sadness and decreased by successful treatment of major depression with an antidepressant. (Reproduced, with permission, from Mayberg et al. 1997.)

Left. Healthy volunteers provided a script of their saddest memory that was later used to generate transient sadness while undergoing positron emission tomography (PET). The rostral anterior cingulate cortex was activated (**red** pseudo-color in the sagittal section of the human brain) was activated when the sad story was read. **Cg25** is an alternative nomenclature for the cingulate gyrus, Brodmann area 25. The PET ligand was oxygen-15–labeled water, used to measure cerebral blood flow as a proxy for brain activity.

Right. Elevated metabolism in the rostral anterior cingulate cortex was confirmed in subjects with major depression. Following successful treatment with a selective serotonin reuptake inhibitor (**SSRI**) antidepressant, brain activity in Cg25 decreased (**blue** pseudo-color in the sagittal section of the human brain). The PET ligand was 2-deoxyglucose, used to measure cerebral metabolism as a proxy for brain activity.

increasing synaptic dopamine, such as amphetamine and cocaine, pose a high risk of overuse and addiction. More recently, tests of drugs that release reward circuits from inhibitory control, such as kappa opiate receptor antagonists, have been initiated in patients with major depression.

A Decrease in Hippocampal Volume Is Associated With Mood Disorders

The best-established structural abnormality in mood disorders is decreased hippocampal volume in individuals with major depression compared with healthy subjects. Recent studies of patients with major depression and bipolar disorder have found hippocampal volume loss in unmedicated subjects in regions of the cerebral cortex associated with the control of emotion. Such studies, which still need replication, show both overlapping and nonoverlapping patterns of volume loss in patients with major depression compared with bipolar disorder. Volume reductions observed in patients with major depression correlate with the duration of depressive episodes when controlling for duration of medication use. These findings suggest that in major depression the volume losses result from persistent illness and do not represent an antecedent risk factor. Some researchers have hypothesized that elevated cortisol levels in patients with major depression might be associated with reduced hippocampal volumes.

Reduced hippocampal volume has also been reported in cases of PTSD. In contrast with major depression, studies of monozygotic twins discordant for PTSD suggest that small hippocampi precede onset of the disorder and may thus represent a risk factor instead of a result of the disorder.

The acquired loss of hippocampal volume in major depression could result from loss of dendrites and dendritic spines, from decreased cell numbers (neurons or glia), or both. Given the relationship of stress and depression, excessive cortisol secretion could play a causal role in either type of loss. A decrease in hippocampal cell number could be explained by the fact that stress and elevated glucocorticoid levels suppress adult hippocampal neurogenesis, as shown in studies of several animal species.

In several mammals, including humans, new granule cells within the dentate gyrus of the hippocampus are produced during adult life. Studies of rodents have shown that these new neurons can be incorporated into functional neural circuits where they initially exhibit heightened structural and synaptic plasticity. A role for cell death as a balance to adult neurogenesis is less well studied.

In rodents, stressful or aversive treatments or administration of glucocorticoids inhibits the proliferation of granule cell precursors and thus suppresses normal rates of neurogenesis in the hippocampus. Antidepressants, including the selective serotonin reuptake inhibitors, exert an opposite effect, increasing the rate of neurogenesis. Thus, excess secretion of glucocorticoid stress hormones, as occurs in depression, could cause hippocampal volume loss by inhibiting neurogenesis over time. Because glucocorticoid receptors in the hippocampus are required for inhibitory feedback to hypothalamic neurons that synthesize and release CRH, impairments of hippocampal function could further impair feedback regulation of the HPA axis, creating a vicious cycle.

The hippocampus permits the brain to resolve differences among closely related stimuli (pattern separation) and provides contextual information that facilitates interpretation of the survival significance of a stimulus. Such information is needed by the organism to accurately identify threats that are signaled within a stream of complex sensory inputs. In animal studies, hippocampal lesions increase anxiety responses; it is thought that the resulting impairment of pattern separation and processing of contextual information permits threat-related memories to generalize inappropriately and thus to become associated with innocuous stimuli. Physiological and behavioral evidence suggests that newborn neurons within the dentate gyrus of the hippocampus play a particularly important role in pattern separation. Thus, inhibition of neurogenesis might contribute to anxiety symptoms that often accompany major depression, and abnormally low hippocampal volumes might increase the risk of PTSD.

Major Depression and Anxiety Disorders Can Be Treated Effectively

Major depressive disorder can be treated effectively with antidepressant drugs, cognitive psychotherapy, and electroconvulsive therapy. Major depressive disorder refractory to other interventions is being treated experimentally with deep brain stimulation targeted to the subgenual prefrontal cortex and other targets, including the nucleus accumbens.

Current Antidepressant Drugs Affect Monoaminergic Neural Systems

Named for their first clinical indication, the antidepressant drugs have broader utility than suggested by their name. Indeed, antidepressants are also the first-line

drugs for the treatment of anxiety disorders. Along with frequent co-occurrence and sharing of risk factors and some neural circuits, the overlap in effective treatment modalities is further evidence that mood and anxiety disorders are related.

All widely used antidepressant drugs increase activity in monoaminergic systems in the brain, most significantly serotonin and norepinephrine, although some antidepressants exert modest effects on dopamine as well. The relevant monoamine neurotransmitters—serotonin, norepinephrine, and dopamine—are synthesized by cells that reside within brain stem nuclei (Chapter 40). Serotonergic and noradrenergic neurons in the pons and medulla project widely to highly diverse terminal fields in brain regions that include the hypothalamus, hippocampus, amygdala, basal ganglia, and cerebral cortex (Figures 61–5 and 61–6). Dopaminergic neurons in the ventral tegmental area and substantia nigra pars compacta of the midbrain project to somewhat less widespread areas. Ventral tegmental neurons project to the hippocampus, amygdala, nucleus accumbens, and prefrontal cortex; substantia nigra neurons innervate the caudate and putamen. The widely divergent projections of these monoaminergic neurons permit them to influence functions such as arousal, attention, vigilance, motivation, and other cognitive and emotional states that require integration of multiple brain regions.

Serotonin, norepinephrine, and dopamine are synthesized from amino acid precursors and packaged into synaptic vesicles for release. Monoamines in the cytoplasm that are outside of vesicles are metabolized by the enzyme monoamine oxidase (MAO), which is associated with the outer leaflet of mitochondrial

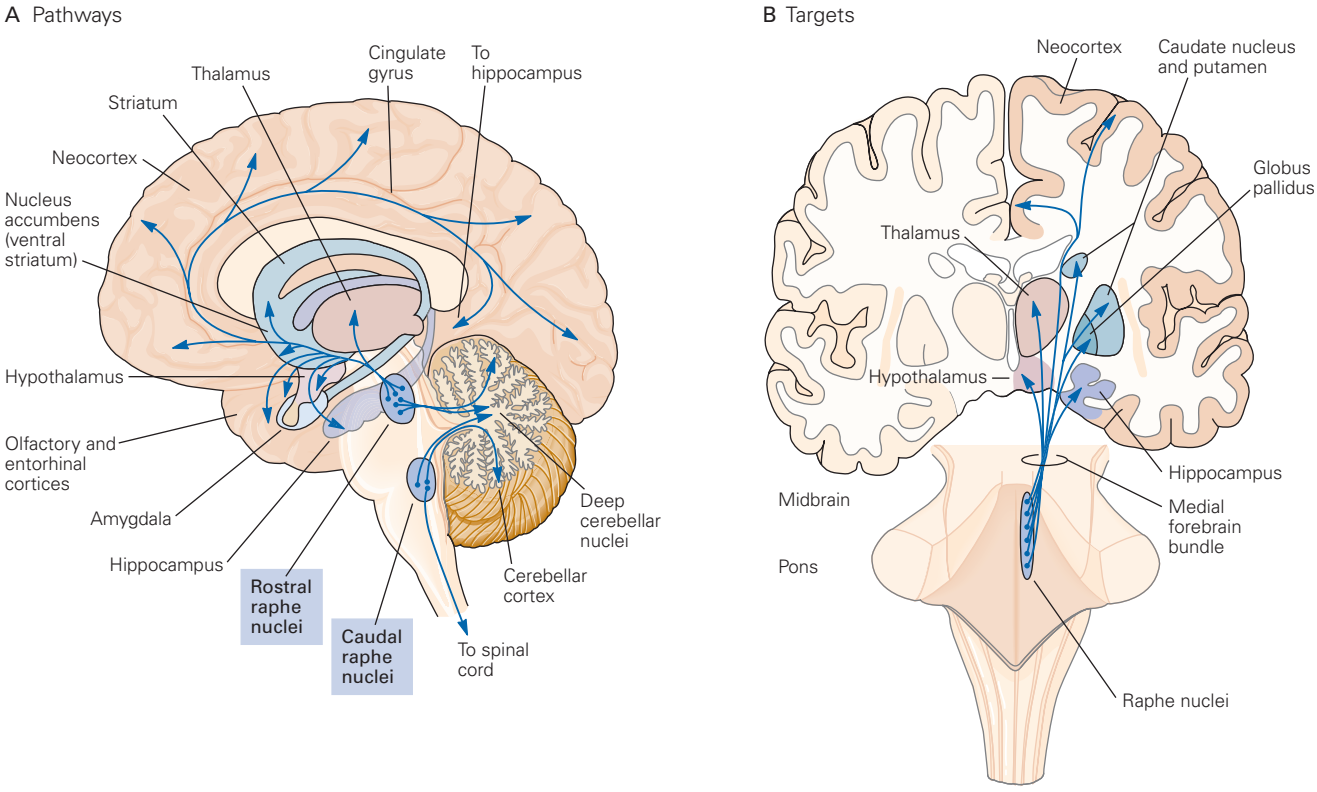


Figure 61–5 The major serotonergic systems in the brain arise in the raphe nuclei of the brain stem. Serotonin is synthesized in a group of brain stem nuclei called the raphe nuclei. These neurons project throughout the neuraxis, ranging from the forebrain to the spinal cord. The serotonergic projections 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 raphe nuclei neurons.

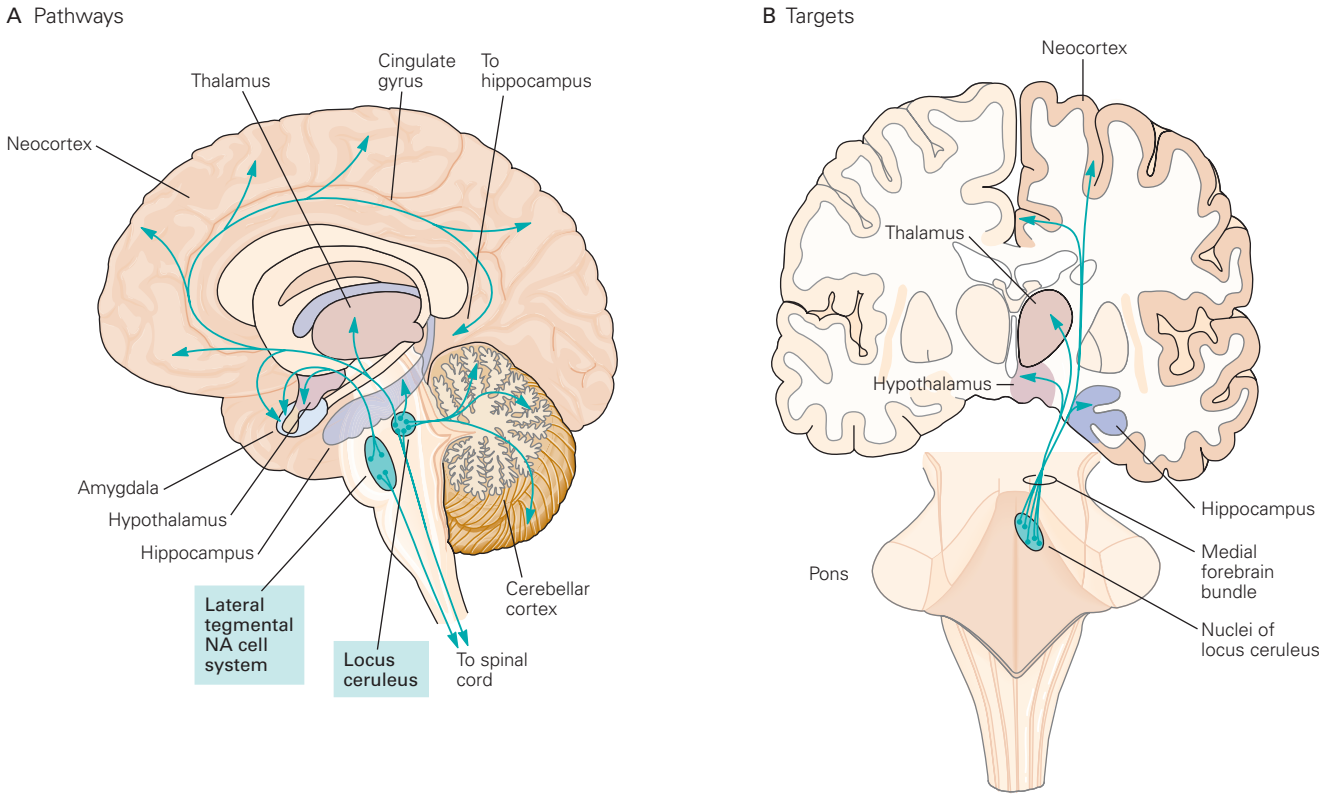


Figure 61–6 The major noradrenergic projection of the forebrain arises in the locus ceruleus. (Adapted, with permission, from Heimer 1995.)

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 (NA) 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.

membranes. After vesicular release, monoamine neurotransmitters bind synaptic receptors to exert their biological effect or are cleared from the synapse by specific transporter proteins located on the presynaptic cell membrane.

The most widely used antidepressant drugs fall into several major groupings, which affect monoaminergic neurons and their targets (Figure 61–7). The *MAO inhibitors* discovered in the 1950s, such as phenelzine and tranylcypromine, are effective against both depression and anxiety disorders but are rarely used today because of their side effects. MAO inhibitors block 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, 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 meats and cheeses. Transporters shuttle these amines into the terminals of sympathetic neurons, where they can displace endogenous vesicular norepinephrine and epinephrine into the cytoplasm, leading to nonvesicular release that causes significant elevations of blood pressure.

The *tricyclic antidepressants*, also first identified in the mid-1950s, include imipramine, amitriptyline, and desipramine; these block the norepinephrine transporter (NET), the serotonin reuptake transporter (SERT), or both. These drugs are effective in treating both depression and anxiety disorders. However, in addition to their therapeutic targets, the older tricyclic drugs also block many neurotransmitter receptors,

including the muscarinic acetylcholine, histamine H_1, and α_1 noradrenergic receptors, producing a panoply of side effects.

The *selective serotonin reuptake inhibitors* (SSRIs) such as fluoxetine, sertraline, and paroxetine, first approved in the 1980s, have no greater efficacy than the older tricyclic antidepressants and MAO inhibitors but are widely used because they have milder side effects and are far safer if taken in overdose. As their name implies, they selectively inhibit SERT. They are effective for major depressive disorder and many anxiety disorders. In high doses, selective serotonin reuptake inhibitors are also effective for symptoms of obsessive-compulsive disorder. Selective norepinephrine and serotonin-norepinephrine reuptake inhibitors have also been developed; these drugs have side effect profiles similar to those of selective serotonin reuptake inhibitors but are useful for some patients who do not benefit from inhibition of SERT alone.

Despite knowledge of the initial molecular targets that mediate the effects of antidepressant drugs, MAO or monoamine transporters, the ultimate molecular mechanisms by which they relieve depression remain unknown. One major challenge to understanding the therapeutic action of these drugs is the delay in their therapeutic effects. Although antidepressant drugs bind to and inhibit MAO, NET, or SERT with their first dose, several weeks of treatment are typically required to observe a lifting of depressive symptoms.

Several hypotheses have been put forward to explain this delay. One is that a slow buildup of newly synthesized proteins alters the responsiveness of neurons in a manner that treats the depression. Another is that increases in the levels of synaptic transmission of serotonin or norepinephrine rapidly increase plasticity in different emotion-processing circuits and that the latency to therapeutic benefit reflects the time it takes for new experiences to alter synaptic weights. A third hypothesis is that antidepressant efficacy is mediated in part by enhancement of hippocampal neurogenesis. Narrowing down the possible therapeutic mechanisms is challenging because of the lack of good animal models of depression. Without an animal model, it is not possible to know which of the many observable molecular, cellular, and synaptic changes cause depression or underlie the therapeutic actions of effective antidepressants.

Ketamine Shows Promise as a Rapidly Acting Drug to Treat Major Depressive Disorder

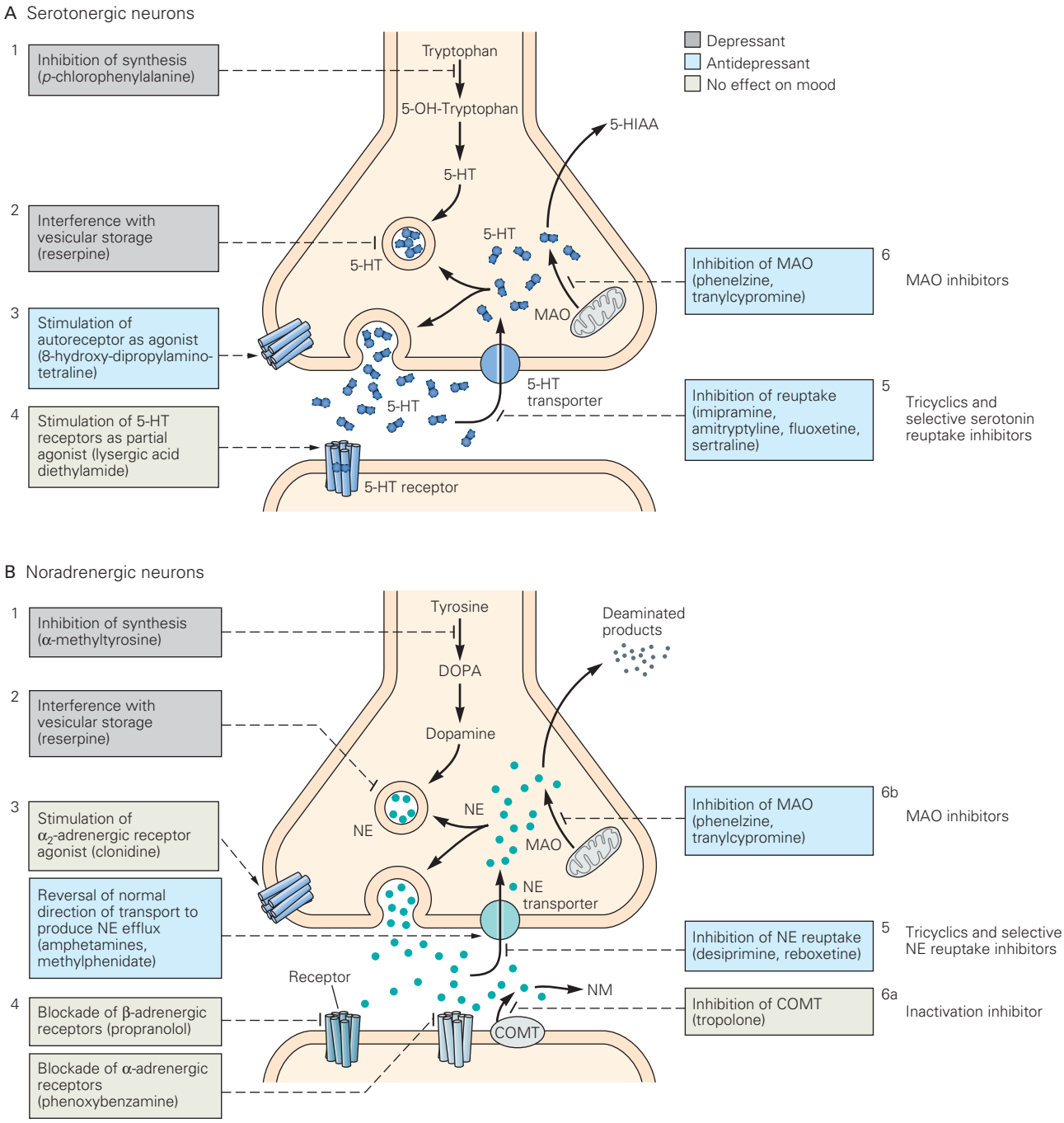
Ketamine, which blocks the *N*-methyl-D-aspartate (NMDA) glutamate receptor, is currently used in pediatric anesthesia for its ability to produce dissociative experiences as well as analgesia. It has been studied in randomized clinical trials with subjects suffering from major depression. In the trials, ketamine was administered by intravenous infusion; it produced an antidepressant effect within 2 hours, a significant advantage over existing antidepressant drugs that typically take weeks to show benefit. The therapeutic effects of ketamine last for approximately 7 days, after which second and third doses may continue to be effective. If such results become widely replicated, ketamine would represent the first antidepressant drug that does not exert its primary action on monoamine neurotransmission. Studies to identify mechanisms by which ketamine relieves depression, like those for older antidepressants, are challenging in part because of the lack of good animal models of depression.

At higher doses, ketamine is misused as a recreational drug to produce euphoria, dissociation, depersonalization, and hallucinations. Ketamine has also been used in laboratory settings to induce cognitive symptoms reminiscent of schizophrenia in human subjects. Although the advantages of a rapidly acting antidepressant would be significant, for example in treating acutely suicidal individuals, the unwanted psychotropic effects of ketamine make its use problematic. Attempts to develop alternative NMDA receptor blockers in which the antidepressant effects might be separated from psychotropic side effects are under way.

Psychotherapy Is Effective in the Treatment of Major Depressive Disorder and Anxiety Disorders

Short-term symptom-focused psychotherapies have been developed for depression and anxiety and tested in clinical trials. The best-studied psychotherapies are the cognitive behavioral therapies. Cognitive therapies that might be used to treat major depression focus on identifying and correcting excessively negative interpretations of events and of interactions with other people. For example, many depressed people exhibit a strong attentional bias toward negative information, automatically interpret neutral events as negative, and read evidence of disapproval into the behavior of others. Such automatic negative thinking, which can initiate or perpetuate depressed mood, can be much improved through cognitive psychotherapies.

Therapies with a more behavioral component have proven useful in the treatment of anxiety disorders such as phobias or PTSD. In exposure therapy, the affected individual is directed to vividly recollect phobic stimuli that trigger anxiety or avoidance. The therapist provides a safe context for such experiences


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 as 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
Inhibition of MAO (phenelzine, tranylcypromine)
6
MAO inhibitors
Inhibition of reuptake (imipramine, amitryptyline, fluoxetine, sertraline)
5
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
Deaminated products
DOPA
Dopamine
NE
NE
MAO
NE transporter
Receptor
NM
COMT
Inhibition of MAO (phenelzine, tranylcypromine)
6b
MAO inhibitors
Inhibition of NE reuptake (desiprimine, reboxetine)
5
Tricyclics and selective NE reuptake inhibitors
Inhibition of COMT (tropolone)
6a
Inactivation inhibitor