Decades of basic and clinical neuroscience research have greatly improved our understanding of the neurobiology of depression. Clinical studies have helped establish which treatments are effective, and have led to evidence-based treatment algorithms that can be readily applied to the “real-world” situation. Basic research has yielded insights into the genetic, molecular, cellular, and neuroanatomical bases of depression. Based on these findings, there is a growing acceptance of depression, and other mood disorders, as diseases of the brain rather than purely aberrations of “mind.” Despite these advances, depression remains a common and inadequately treated illness, with few strategies for prevention or cure. The lifetime prevalence of depression approaches 17% in the United States, and depression is recognized to be one of the leading causes of disability worldwide. Available treatments for depression—including pharmacotherapy, evidence-based psychotherapy, and electroconvulsive therapy (ECT)—are effective in reducing symptoms in the majority of patients with an acute depressive episode, and the combination of these treatments may be more efficacious than individual treatments alone. However, up to 40% of patients continue to have clinically significant symptoms despite optimized treatment, and up to 20% of patients may show little to no response to the most aggressive management (including the use of ECT). Even for patients who do respond to treatment, the illness tends to be highly recurrent, with up to 80% of patients experiencing at least one subsequent episode. Psychotherapy and/or maintenance antidepressant medications may substantially decrease the risk of relapse.
but do not eliminate it.\textsuperscript{11}

In the face of these clear challenges, the continued neurobiological investigation of depression offers reason for optimism. Based on a solid foundation, basic and clinical neuroscience research is progressing rapidly, with many exciting developments on the horizon. Importantly, as the pathophysiology of depression becomes better understood, a number of novel treatment targets are being identified. These treatments promise to offer unique mechanisms of action that will likely allow clinicians to improve on the current rates of response and remission. Further, as the factors that contribute to the development of depression are better described, there is hope that effective preventive and curative strategies may eventually be developed, as well as predictors of response to one treatment versus another being identified.

In this review, we discuss a number of these exciting potential directions for future research in depression. We begin with a review of the role of monoamine circuit dysfunction in depression and describe some avenues for further research on these neurotransmitter systems. We then discuss the putative role of neuroendocrine and neuropeptide systems and some novel treatment strategies involving these systems. A number of other neuromodulatory systems are then reviewed briefly, again with a focus on novel drug development. We conclude with a discussion of the neuroanatomical basis and neural network theories of depression, emphasizing recent developments in neuroimaging and focal brain stimulation.

### Monoamine neurotransmitter systems

Monoamine deficiency is among the oldest of the neurochemical theories of depression,\textsuperscript{12,13} with much research over the last four decades focused on monoaminergic function. The monoamine neurotransmitter systems—including serotonin, norepinephrine (NE), and dopamine—are widely distributed throughout the central nervous system and are involved in the regulation of many aspects of behavior including mood, cognition, locomotion, sleep, appetite, libido, arousal, anxiety, and aggression. The monoamine systems largely function as modulators of excitatory and inhibitory neurotransmitter circuits. Although each neurotransmitter system appears to regulate a distinct cluster of functions, considerable overlap exists between these systems. Each is reviewed below.

#### Serotonin

Serotonin (5-HT) is produced in cells of the rostral and caudal raphe nuclei. Serotonergic projections are widespread throughout the central nervous system (CNS) and include several brain regions implicated in the pathophysiology of depression, including the hypothalamus, thalamus, hippocampus, amygdala, basal ganglia, prefrontal cortex, and cingulate cortex. The effects of serotonin are mediated through pre- and postsynaptic 5-HT receptors; to date, at least 13 molecular subtypes of 5-HT receptors have been identified. Among these subtypes, three major families of receptors have been linked to depression: 5-HT\textsubscript{1A/B}, 5-HT\textsubscript{2A/C}, and 5-HT\textsubscript{3}. After release from the presynaptic nerve terminal, 5-HT binds to 5-HT receptors or is taken up into the presynaptic terminal by the serotonin transporter (SERT) and either repackaged into a terminal vesicle or catabolized by monoamine oxidase (MAO).

Serotonergic dysfunction has been clearly and consistently linked with most, if not all, forms of depression.\textsuperscript{14} Cerebrospinal fluid (CSF) levels of serotonin metabolites—primarily 5-hydroxyindole acetic acid (5-HIAA)—are generally reduced in depressed patients\textsuperscript{15,16} and are even lower in depressed patients with a history of suicide attempts.\textsuperscript{14} Tryptophan depletion can lead to a depressive relapse in euthymic patients with a history of depression responsive to selective serotonin reuptake inhibitors (SSRIs).\textsuperscript{17,18} SERT availability has been shown to be reduced in several brain regions in patients with major...
depression, though discordant findings have appeared. Abnormalities in SERT binding have been consistently identified in depression. Of paramount importance, all SSRIs are efficacious in the treatment of depression, and are generally considered first-line treatment for the illness. Many of the effects of serotonin on mood and behavior are thought to be mediated through action at postsynaptic 5-HT₂ receptors. In unmedicated suicide victims with depression, an increased density of 5-HT₂ receptors has been reported in the prefrontal cortex and amygdala, and, similar to findings with SERT, in platelets. Treatment with antidepressant medications is generally associated with decreased density of 5-HT₂ receptors over a time course that corresponds to the onset of antidepressant efficacy — this finding suggests that upregulation of 5-HT₂ receptors in depression may be a compensatory response to a chronically low serotonergic state. However, other data suggest that 5-HT₂ receptor activity may not completely normalize with antidepressant treatment. Also, using a radiolabeled positron emission tomography (PET) ligand for the 5-HT₂ receptor, Biver et al found reduced 5-HT₂ activity in the right orbitofrontal and insular cortices. Another group found no difference in 5-HT₂ activity in depressed patients versus normal controls; however, this study excluded subjects with suicidal ideation.

Depression is a highly heritable illness, with one third of the risk for developing the disorder explained by genetic factors and two thirds of the risk attributable to the environment. A growing database suggests that the relationship of serotonin function and depression may be modulated in part by a gene-environment interaction. An early study showed an association between depression and a functional polymorphism of the promoter region for the SERT gene (5-HTTLPR). The 5-HTTLPR has two alleles: a “short” (s) version and a “long” (l) version; presence of an s allele is associated with a functionally significant decrease in SERT activity. Other studies have shown an association between the presence of the s allele and the personality trait of neuroticism. A landmark study demonstrated that the 5-HTTLPR polymorphism moderated the influence of stressful life events on the development of depression. Specifically, this study showed that individuals homo- or heterozygous for the s allele were more likely to develop depressive syndromes after exposure to childhood abuse or neglect compared with subjects homozygous for the l allele. At least two large-scale studies have replicated this finding, although not all studies are consistent. Some studies have suggested this gene-environment interaction may be stronger in females than males.

Norepinephrine

Norepinephrine (NE) is primarily produced in cells of the pontine locus ceruleus. Similar to 5-HT neurons, these cells project to multiple cortical and subcortical brain regions, many of which have been implicated in the biology of depression. The NE system is well known to modulate the stress response, and the locus ceruleus receives inputs from several other neurotransmitter systems providing information about homeostasis (eg, 5-HT, opioids, γ-aminobutyric acid [GABA], corticotropin-releasing factor [CRF], DA, and glutamate). Norepinephrine exerts its effects through interaction with pre- and postsynaptic α- and β-adrenergic receptors. Similarly to 5-HT, following release from the presynaptic nerve terminal, NE is taken back up into the presynaptic terminal by the norepinephrine transporter (NET) where it is either repackaged or metabolized by MAO. A role for NE in the pathophysiology of depression is fairly well-established but less clear than for 5-HT. Administration of drugs that deplete NE stores (such as reserpine) can precipitate depressive symptoms — however, such drugs affect stores of other neurotransmitters such as 5-HT and DA. Studies of NE metabolite levels (primarily 3-methoxy-4-hydroxy-phenylglycol [MHPG]) in the CSF of depressed patients have yielded inconsistent results. Currently, radioligands for the majority of NE receptors and the NET are not available for use in humans. However, depletion of NE in depressed patients taking noradrenergic antidepressants can result in depressive relapse. Further, depleting NE (as well as DA) in euthymic, unmedicated patients with a history of depression can precipitate a relapse. Suicide victims have been reported to exhibit increased activity of tyrosine hydroxylase, the enzyme that controls the rate-limiting step of synthesis of NE in the locus ceruleus. Drug-free depressed patients exhibit a blunted growth hormone response to clonidine, an α₂-adrenergic agonist. A role for the NE system in depression is further supported by data on the effects of antidepressant medications in humans and animal models. Selective NE reuptake inhibitors (eg, maprotiline, desipramine, and reboxetine) have all been shown to be efficacious in the
treatment of depression. Many tricyclic antidepressant (TCA) medications inhibit both NE and 5-HT uptake, including imipramine. So-called non-TCA “dual” reuptake inhibitors, such as duloxetine and venlafaxine, inhibit reuptake of both 5-HT and NE, are effective in treating depression, and have been suggested to be more efficacious overall than certain SSRIs, though this remains a controversial area. Chronic administration of antidepressant medications or electroconvulsive shock (ECS) are associated with increased noradrenergic neurotransmission.

Dopamine

Dopamine (DA) neurotransmission is primarily organized into three distinct systems within the brain: (i) the nigrostriatal pathway in which DA is produced in the A9 cells of the substantia nigra with projections to the dorsal basal ganglia; (ii) the mesolimbic-mesocortical pathway in which DA is produced in A10 cells in the ventral tegmental area (VTA) of the midbrain with projections to the ventral striatum, other limbic regions (mesolimbic pathway) and prefrontal cortex (mesocortical pathway); and (iii) the tuberoinfundibular pathway in which DA is produced in A12 cells of the arcuate nucleus of the hypothalamus with projections to the intermediate and neural lobes of the pituitary. Three other DA systems have also been described: (i) a periventricular system arising from the dorsal motor vagus nuclei, nucleus of the solitary tract, periaqueductal and periventricular gray, and projecting to midbrain structures including tegmentum, tectum, thalamus, and hypothalamus; (ii) an olfactory bulb system arising from the periglomerular cells in the olfactory bulb; and (iii) an incertohypothalamic circuit from the zona incerta to the hypothalamus.

DA exerts effects at DA receptors, of which several subtypes have been identified, and, similarly to 5-HT and NE, DA is taken up into the presynaptic terminal via a DA transporter (DAT). Interestingly, DA nerve terminals in the prefrontal cortex of humans and other primates contain no DAT, and the DA signal is inactivated by uptake into nearby NE nerve terminals by NET. For this reason, NE reuptake inhibitors increase DA availability in the prefrontal cortex. Along with 5-HT and NE, DA is catabolized by MAO. DA is a precursor for NE, but its role in depression has been far less scrutinized. CSF concentrations of the major metabolite of DA—homovanillic acid (HVA)—are decreased in depressed patients, and urine levels of 3,4-dihydroxyphenylacetic acid (DOPAC; another metabolite of DA) have been shown to be decreased in depressed patients and potentially associated with suicidal behavior. There is evidence from both brain imaging studies of the DAT and postmortem studies that DA neurons are reduced in activity in depression. Depression is highly comorbid with Parkinson’s disease, which is characterized by loss of DA cells in the substantia nigra and VTA; however, it should be noted that 5-HT and NE systems are also disrupted in Parkinson’s disease. Monoamine oxidase inhibitors (MAOIs), which have demonstrated efficacy in treating depression, decrease catabolism of all monoamines including DA. Certain medications that primarily affect the DA system, such as psychostimulants and pramipexole, also have antidepressant efficacy, particularly in bipolar depression.

Future directions for monoamine systems research

The monoamine deficiency hypothesis of depression has remained dominant for many years. However, treatments based solely on this hypothesis have proven to be only moderately effective. As the neurobiological understanding of depression matures, it is increasingly clear that a “simple” monoamine hypothesis of depression is inadequate.

Future research will help clarify the role of the monoamines in depression within the context of a larger genetic-neurochemical-neuroanatomical-environmental framework. Although discussed separately, it should be recognized that the 5-HT, NE, and DA systems interact to modulate neural function. For example, 5-HT neurons have synapses on locus ceruleus cells and NE neurons innervate cells in the raphe nuclei. Further, it is clear that the monoamines operate within a larger neurochemical-neuroanatomical system. As discussed below, several brain regions have been implicated in depression, including the hippocampus. In animal models, chronic treatment with antidepressants increases the rate of neurogenesis within the hippocampus, suggesting that site-specific action of these medications may be important. Gene-environment studies suggest that genetic determinants of monoamine function such as SERT polymorphisms determine the degree to which environmental stressors affect one’s vulnerability to depression. Future studies of the monoamines in depression will
focus on a number of areas. Better delineation of the interactions within the monoamine systems will help clarify the specific role of each system in the pathophysiology of depression. Prior studies suggest that some patients respond well to medications that selectively modulate 5-HT function, others respond to medications that affect 5-HT and NE function, while still others appear to require modulation of all three monoamine systems (eg, via MAOIs). Several pharmaceutical companies are developing “triple” reuptake inhibitors which inhibit reuptake of all three monoamines. Studies exploring the interactions between the monoamine systems and other neurotransmitter/neuromodulatory systems (eg, CRF, neuropeptides, glutamate, and GABA—discussed in more detail below) will help develop realistic, integrated neurochemical models of depression. Functional imaging studies combined with neurochemical challenge will help clarify the anatomical specificity of monoaminergic dysfunction in depression. For example, PET imaging can be combined with monoamine depletion strategies to investigate the functional neuroanatomy of depressive relapse with decreased monoamines. Development of radioligands for various monoamine receptors and transporters will help identify in which brain regions and to what degree these systems are abnormal in patients with depression. Genetic studies will also be more informative by incorporating imaging approaches. To date, at least two studies have suggested that 5-HTTLPR polymorphisms affect the structure, function, and functional connectivity of brain regions implicated in the pathophysiology of depression. Recently, we reported that NET polymorphisms predict response to milnacipran, a dual 5-HT/NE reuptake inhibitor, but not fluvoxamine, an SSRI. Future studies will help identify whether this has potential etiologic meaning in depression; also, it is likely that other genetic variations will be identified and investigated in similar fashion.

**Neuroendocrine systems**

The potential contribution of dysfunction of the endocrine system to the neurobiology of depression has long been recognized. Most research has focused on the hypothalamic-pituitary-adrenal (HPA) axis and, to a lesser degree, on the hypothalamic-pituitary-thyroid (HPT) axis.

**HPA axis**

In vulnerable individuals, psychological and physiological stress has long been known to precipitate or worsen depressive episodes. The HPA axis is the primary neuroendocrine system responsible for coordinating the mammalian stress response, and has thus been a major focus of research into the neurobiology of depression. Its major components include corticotropin-releasing factor (CRF), adrenocorticotropin hormone (ACTH) and glucocorticoids; cortisol is the major glucocorticoid in humans. During the stress response, neurons in the paraventricular nucleus (PVN) of the hypothalamus release CRF into the hypothalamo-hypophysial portal system. CRF then stimulates adrenocorticotropin (ACTH) release from the anterior pituitary into the systemic circulation, which in turn stimulates the adrenal cortex to secrete cortisol. Cortisol is responsible for many of the physiological changes associated with the stress response, and also provides negative feedback to the hypothalamus and pituitary to decrease synthesis and release of CRF and ACTH.

Quite distinct from the HPA axis is the widespread CNS distribution of CRF and CRF receptors that includes several cortical, subcortical, and brain stem regions. Importantly, these CRF systems modulate the autonomic, immunologic, and behavioral responses to stress. Two main CRF receptor subtypes have been identified (CRF₁ and CRF₂) which appear to have differential effects on behaviors related to mood and anxiety. CRF₁ receptors have a high affinity for CRF, and are widely distributed in the CNS, and reduced anxiety in animal models is associated with reduced activity of these receptors. In contrast, CRF₂ receptors have a lower affinity for CRF, have a widespread distribution with limited overlap with that of CRF₁ receptors, and reduced CRF₂ activity has been linked with increased anxiety-like behaviors in animals. The HPA axis is abnormally active in patients with depression. CSF CRF concentrations are elevated in drug-free depressed patients compared with controls, and CRF mRNA expression and the number of CRF-containing neurons in the PVN are increased in depressed patients. CRF concentrations are elevated in the frontal cortex of depressed patients, and there is a corresponding reduction in CRF₁ receptors in suicide victims in this area. Further, antidepressants modify CRF activity. In a group of healthy volunteers, desipramine
Basic research

was shown to decrease CSF CRF concentrations, and both fluoxetine and ECT have been reported to produce similar changes in depressed patients. These data point to a potentially critical role for CRF in the pathophysiology of depression.

Some data suggest that particular subtypes of depression may be associated with unique HPA axis abnormalities. Patients with psychotic depression demonstrate significant HPA axis hyperactivity and show the highest rates of HPA axis nonsuppression during the dexamethasone suppression test (DST). Conversely, patients with nonpsychotic depression may demonstrate evidence of decreased or normal HPA axis activity. Depressed patients with a history of early life stress show elevated plasma ACTH and cortisol concentrations in response to a laboratory stressor, whereas depression patients without such a history do not. In one large treatment study of chronic depression, subjects with a history of childhood trauma responded preferentially to a form of cognitive-behavior therapy (CBT) over pharmacotherapy with the antidepressant nefazodone, suggesting that subtypes of depression related to altered stress response may have important treatment implications.

In view of these findings, considerable interest has focused on developing novel antidepressant medications that target the HPA axis directly, and this promises to be an exciting direction for future research in depression. To date, selective CRF$_1$ receptor antagonists have received the most attention, though CRF$_2$ agonists might offer another useful target. Several CRF$_2$ antagonists are in various stages of development (see Gutman et al. for a review). The effects of only one agent, R121919, have been published. Although this agent showed evidence of antidepressant and anxiolytic activity in depressed patients, liver toxicity has eliminated it as a viable novel drug candidate. Current and future studies will assess the antidepressant properties of a variety of CRF$_1$ and possibly CRF$_2$ antagonists.

Other antidepressant treatment strategies based on HPA axis modulation include glucocorticoid synthesis inhibitors and glucocorticoid receptor blockade. Drugs that interfere with cortisol synthesis (eg, ketoconazole, aminoglutethimide, and metyrapone) have potential antidepressant effects; however, data are limited and the unfavorable side effects of these agents limit their potential utility. The glucocorticoid receptor antagonist mifepristone (RU486)—a selective type II glucocorticoid receptor antagonist—has shown modest antidepressant effects in chronic depression, and encouraging effects in the treatment of psychotic depression. Of interest, the positive effects of mifepristone were demonstrated within 1 week of treatment, and the greatest effects were on the psychotic symptoms, not the core symptoms of depression. Given the high rate of HPA axis hyperactivity in psychotic versus nonpsychotic depression, this suggests an important potential mechanism of action specific to psychosis in depression.

Future studies in depression will further explore these findings, and promise to add an important group of medications to the treatment repertoire for depression. Beyond this, research is currently under way to delineate the epidemiological, biochemical, and genetic factors that mediate the effects of psychosocial stress on depressive syndromes. An important aspect of this research will be to better define the interaction between the HPA axis and the monoamine neurotransmitter systems, especially given the apparent role of serotonin neurotransmission in modulating the effects of stress on the development of depression (see above). For example, we recently reported that 5-HT depletion in humans is associated with dramatic increases in CSF CRF concentrations, demonstrating an important 5-HT-CRF link.

HPT axis

Hypothyroidism is classically associated with a depressive syndrome that is ameliorated by correcting the underlying thyroid hormone deficit. This suggests a relation between the hypothalamic-pituitary-thyroid (HPT) axis and the neurobiology of depression. In the HPT axis, thyrotropin-releasing hormone (TRH) is secreted by the hypothalamus and stimulates thyroid-stimulating hormone (TSH) release from the pituitary. TSH acts on the thyroid to stimulate iodine uptake, follicle cell metabolism, and release of the two thyroid hormones (triiodothyronine [T$_3$] and thyroxine [T$_4$]). Thyroid hormones are responsible for a number of homeostatic and metabolic functions and also provide feedback to the hypothalamus and pituitary to decrease further TRH and TSH release, respectively.

A mixed database supports some role for the HPT axis in the pathophysiology of depression. In depressed patients, CSF TRH has been shown to be elevated (suggesting decreased feedback from thyroid hormones) compared with controls, though discordant findings have been reported. Several studies have revealed a
blunted TSH response to TRH stimulation in depressed patients despite normal thyroid hormone levels, consistent with downregulation of TRH receptors in the pituitary, perhaps secondary to elevated TRH levels. Alternatively, thyroid hormone in the periphery may not be efficiently transported into the CNS in depressed patients; CSF levels of transthyretin—the protein responsible for transporting thyroid hormones across the blood-brain barrier at the choroid plexus—have been shown to be decreased in depressed patients. Thyroid hormone augmentation (primarily with T3) has been reported to exert antidepressant effects, even in the absence of clinical hypothyroidism, through several negative studies are available (P. Ninan and C. B. Nemeroff, unpublished observations). Future studies will help clarify the role of the HPT axis in the pathophysiology and treatment of depression. As with the HPA axis, areas of interest include the interaction of the HPT system with other neuromodulatory systems. Of particular interest is whether patients with subclinical hypothyroidism, such as symptomless autoimmune thyroiditis, or particular subtypes of depression are more likely to respond to thyroid augmentation.

**Other neuromodulatory systems**

In addition to the monoamines and constituents of the neuroendocrine systems, there are a number of other neuromodulators that have been implicated in the neurobiology of depression. Increasing research efforts have focused on these systems, especially as potential targets for novel drug development. In general, future studies will help clarify the role of these systems in the pathophysiology and treatment of depression. In particular, the relation between these systems and other neurotransmitter systems will need to be better delineated. Also, given the general lack of anatomic specificity for some of these systems (such as glutamate and GABA), drug development will need to focus on agents that show potential antidepressant efficacy without additional unwanted adverse effects. A promising new direction in pharmacological research involves the system implicated in circadian rhythms. Agomelatine, which acts as an agonist at melatonin MT1/MT2 receptors and an antagonist at 5HT2c receptors, has proven its antidepressant efficacy in clinical trials, and has a favorable tolerability profile.

**Glutamate**

Glutamate is the primary excitatory neurotransmitter in the brain. Glutamate receptors are divided into two types: ionotropic (including the N-methyl-D-aspartate [NMDA], α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [AMPA], and kainite receptors) and metabotropic (including a family of G-protein coupled receptors associated with adenylyl cyclase and phosphoinoside second messenger systems). Excitatory glutamatergic neurotransmission likely plays a role in depression. Indeed, stress may contribute to depression by increasing excitatory glutamatergic neurotoxicity in brain areas involved in mood regulation. Sanacora et al reported that depressed patients had higher cortical glutamate levels compared with healthy controls, using magnetic resonance spectroscopy. Ionotropic glutamate receptor antagonists can decrease stress-induced loss of hippocampal neurons, and data suggest amantadine (a nonselective NMDA receptor antagonist) may enhance antidepressant-like effects of typical antidepressants in animal models and depressed patients. Preclinical studies of selective NMDA receptor antagonists have revealed antidepressant-like effects in animal models. Additionally, agents that enhance AMPA receptor function may augment antidepressant effects of standard antidepressant medications. Riluzole, which inhibits glutamate release, has shown preliminary antidepressant effects in patients with bipolar depression, but no placebo-controlled data are available and effects in unipolar depression have not been studied.

**GABA**

GABA is the major inhibitory neurotransmitter in the CNS. There are two major types of GABA receptors: GABA_A and GABA_B. GABA_A receptors are chloride channels and contain the binding site for benzodiazepines. GABA_B receptors are coupled to calcium channels. A role for GABA in the pathophysiology of depression has long been postulated, and several recent studies support this hypothesis. Preclinical studies have demonstrated decreased CNS GABA concentrations in animal models of depression. CSF and plasma GABA concentrations have been reported to be decreased in depressed patients. Postmortem investigation of the hippocampus in depressed patients suggested possible GABAergic dysfunction. GABA_B receptors are found on most 5-HT-
containing neurons in the dorsal raphe, and GABA release into the dorsal raphe decreases firing of 5-HT neurons. Modulating GABA function has been shown to have important behavioral effects in animal models, with GABA antagonists demonstrating certain antidepressant-like properties. Using magnetic resonance spectroscopy, Sanacora et al demonstrated decreased GABA concentrations in the occipital cortex of depressed patients. Moreover, this group showed GABA concentrations increase in the occipital cortex after SSRI treatment and ECT, but not after CBT. CNS GABA concentrations have also been shown to be normal in remitted depressed patients compared with controls.

Neurokinins

Neurokinins are neuropeptides widely distributed in the CNS and peripheral nervous system, and are believed to play a role in nociception. Substance P is the most abundant neurokinin in humans and is found in neurons in several brain regions implicated in the neurobiology of depression. Substance P is also colocalized in cells containing 5-HT and NE. Substance P binds to several receptor subtypes (NK-1, NK-2, NK-3, NKA, NKB), and appears to have an important role in modulating the mammalian stress response. In animal models, substance P results in behavioral and physiologic changes characteristic of a stress response. These changes can be attenuated by substance P antagonists. Supporting its role in depression, CSF substance P concentrations were reported to be elevated in depressed patients compared with controls, and lower serum concentrations of substance P have been correlated with better antidepressant treatment response. Our group has reported elevations in CSF substance P concentrations in drug-free patients with major depression and PTSD.

One placebo-controlled study using a neurokinin receptor (NK-1) antagonist (MK-869) suggested efficacy in treating depression, but several follow-up studies found no significant antidepressant effects for this agent. Two other selective NK-1 receptor antagonists (L-759274 and CP-122721) have shown potential efficacy in treating depression, although data are relatively limited. In general, these drugs appear to be well-tolerated.

Neuroanatomical models

Several lines of evidence support a neuroanatomical basis for depression. Brain regions consistently implicated in the neurobiology of mood regulation and depression include the prefrontal cortex (including dorsolateral, ventromedial, and orbitofrontal portions), cingulate cortex (primarily the ventral anterior cingulate and subgenual cingulate), thalamus, amygdala, hippocampus, ventral striatum, portions of the temporal and parietal cortices, and various midbrain and brain stem nuclei. The data supporting a role for these brain regions in depression has been extensively reviewed elsewhere, and primarily include studies of depression in neurological disease (such as Parkinson’s disease, Huntington’s disease, Alzheimer’s dementia, and traumatic brain injury including stroke), neuropathological studies in depressed patients, and neuroimaging studies. On a histological level, evidence suggests a number of microstructural abnormalities in depression, including defects in neuronal and glial cell structure and white matter integrity.

As data have accumulated, increasingly complex models of mood regulation have been developed. These models are largely based on the premise that widely distributed brain regions are structurally and functionally connected such that their coordinated activity is required for normal mood regulation. Thus, there is less emphasis on the function of a specific brain region in isolation, and more weight given to how multiple brain regions function together. Depression, and other mood disorders, are then characterized by network dysfunction (ie, abnormalities in the coordination of two or more brain regions).

Neural network models of depression form the basis for several exciting directions for future mood disorders research. It is expected that neuroimaging methods will continue to become more sophisticated and better describe the structure and function of the brain in depressed patients at various stages in the illness (eg, prior to treatment, in remission, or during treatment resistance). Novel uses of neuroimaging (many of which have been mentioned in previous sections) include receptor/transporter imaging, combined pharmacology-imaging studies, neurochemical challenge studies, and functional imaging studies (both resting state and task-activated). Diffusion tensor imaging (DTI) provides information on the integrity of white matter tracts and can be used for tractography; such studies may help correlate abnormalities in functional connectivity in depression with abnormalities in structural connectivity. Combination of imaging with other research methods (eg, genetic, neuroendocrine, and focal brain stimulation...
[discussed below]) may eventually help provide detailed multifactorial “profiles” of depressive subtypes.

Another research direction that has both developed out of, and contributed to, neural network theories of depression is focal brain stimulation. Focal brain stimulation techniques (including transcranial magnetic stimulation [TMS], vagus nerve stimulation [VNS] and deep brain stimulation [DBS]) are designed to provide direct, modifiable stimulation to a specific brain region with the goal of modulating function throughout a particular neural system. Over the last several years, these techniques have been used increasingly to study the neurobiology of depression and as potential antidepressant therapies.

**Transcranial magnetic stimulation**

Transcranial magnetic stimulation (TMS) uses a current passed through an electromagnetic coil on the scalp to create a brief, rapidly changing magnetic field. This magnetic field experiences little to no impedance from the scalp, skull and air, and is able to induce a small, focal electrical current within the underlying cortex, resulting in depolarization of cortical neurons. Although single-pulse TMS is an established diagnostic and research tool in humans, repetitive TMS (rTMS) has been most extensively studied as a possible treatment for depression. By convention, high-frequency or “fast” rTMS refers to stimulation delivered at a rate higher than 1 Hz, and low-frequency or “slow” rTMS refers to stimulation at frequencies of 1 Hz or slower. No anesthesia is needed when giving rTMS (except in the case of magnetic seizure therapy [MST] discussed separately below).

rTMS has been associated with behavioral changes in animals similar to those achieved with electroconvulsive shock and suggestive of an antidepressant effect, and functional imaging studies have confirmed that TMS can modulate function in several brain regions (including subcortical structures) implicated in mood regulation. Several studies have shown antidepressant effects for fast rTMS applied to the left dorsolateral prefrontal cortex; a smaller number have shown efficacy for slow rTMS applied to the right dorsolateral prefrontal cortex. Although meta-analyses of these studies generally agree that rTMS appears to have statistically significant antidepressant effects, the clinical significance of these effects has yet to be convincingly demonstrated. rTMS appears to be safe and reasonably well-tolerated. Magnetic seizure therapy (MST) uses a modified rTMS system to induce a generalized seizure similar to that obtained with ECT. The goal is obtain the same efficacy as with more focal forms of ECT (eg, right unilateral lead placement) but with fewer cognitive side effects. Indeed, there is some preliminary data to support an antidepressant effect for MST with fewer cognitive side effects compared with ECT, but confirmatory data are lacking. Future studies will help clarify whether TMS offers a clinically useful treatment alternative in depression. However, even if TMS proves to be ineffective as an antidepressant treatment, it will likely continue to be useful as a probe of neural function, especially when combined with neuroimaging. When combined with imaging of regional blood flow or glucose metabolism, TMS can be used to better define the degree of functional connectivity between brain regions involved in mood regulation. Combined with neurochemical imaging (such as receptor imaging), TMS can be used to probe the role of specific neurotransmitter systems.

**Vagus nerve stimulation**

Vagus nerve stimulation (VNS) uses a programmable electrical stimulator to provide intermittent stimulation to a patient’s left vagus nerve. VNS was originally FDA-approved for treatment-resistant epilepsy and was recently approved for the adjunctive treatment of a major depressive episode that has not responded to at least four antidepressant medication trials. Mood improvements have been reported by epileptic patients receiving VNS, and one open and one double-blind study have shown antidepressant efficacy for VNS in depressed epilepsy patients. A single open study of VNS in 60 nonepileptic patients with treatment-resistant depression found a 31% response rate and 15% remission rate after 10 weeks; response and remission were generally maintained after at least 1 year of treatment and showed further increases after 2 years of treatment. However, a large, sham-controlled study failed to show statistically significant antidepressant effects for active VNS after 10 weeks of treatment. After 1 year of active VNS (all sham-treated patients received active VNS after the initial 10-week evaluation period), the response rate increased to 27% and remission rate was 16%. These

*Editor's note: see also the article by Eitan and Lerer (this issue, p 241) for a detailed review of these techniques.
1-year response and remission rates were better than those in a medication management, observation-only comparison group of similarly treatment-resistant patients followed for a similar period of time (13% response and 7% remission in the observation-only group). Longer-term response, remission, and relapse data are not currently available for this group of patients. Generally, VNS is safe, well-tolerated, and acceptable to patients. The body of data, taken together in this very refractory patient population, was sufficient to lead to FDA to approve VNS for the treatment of pharmacoresistant depression.

The potential mechanism(s) of action of VNS are not fully understood. The central projections of the vagus nerve via the nucleus tractus solitarius innervate multiple brain areas implicated in mood regulation, and functional brain imaging studies have confirmed that VNS alters activity of many of these cortical and subcortical regions. VNS may affect function of GABA, DA, and NE, though conflicting data have been reported. These neurotransmitter system effects have not been consistently associated with therapeutic response.

Deep brain stimulation

Deep brain stimulation (DBS) involves a small electrical stimulator implanted into a defined brain location which typically provides chronic stimulation. Bilateral DBS of the subthalamus or globus pallidus is an accepted treatment for refractory Parkinson’s disease, and can be associated with significant mood changes in patients with Parkinson’s disease. A single open study reported effects of bilateral high-frequency DBS of the white matter adjacent to the subgenual cingulate cortex in six highly treatment-resistant depressed patients (five of whom had failed ECT). In this study, four of the six patients showed an antidepressant response at the 6-month study end point, with three in remission and the fourth near remission. No significant adverse events were noted. In this study, antidepressant response was associated with regional blood flow changes in brain regions clearly implicated in the pathophysiology of depression (dorsolateral prefrontal cortex, subgenual cingulate, perigenual anterior cingulate, hypothalamus, brain stem). DBS appears to modulate function within discrete neural networks, although its actual mechanisms of action are largely obscure. DBS may help restore normal neural network function by decreasing function in abnormally active “nodes” by activating dormant compensatory mechanisms, or by some combination of these two. If DBS is confirmed to be an effective treatment for some patients with depression, further investigation of its mechanisms of action may greatly improve our understanding of the neurobiology of normal and abnormal mood regulation.

Conclusion

Depression remains a prevalent and somewhat difficult-to-treat disease despite decades of neurobiological research and significant advances in the understanding of its pathophysiology. Current and future research efforts promise to further expand our knowledge of the biological bases for depression and will likely contribute a number of new antidepressant treatments. These prospective treatments include several novel drugs targeting neuromodulatory systems beyond the monoamines and focal brain stimulation techniques which directly target neural networks involved in depression. Over the next several years, we expect significant advances to occur in our understanding and treatment of depression.

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## Perspectivas futuras en la investigación de la depresión

La depresión mayor es una enfermedad común, incapacitante y a menudo difícil de tratar. Décadas de investigación en la neurobiología y la terapéutica de la depresión han permitido avanzar de manera importante en nuestra capacidad para manejar este trastorno. Sin embargo, persisten diversos desafíos. Un número significativo de pacientes depresivos no consiguen una remisión completa, a pesar de optimizar los tratamientos. Para los pacientes que logran la resolución de los síntomas, la depresión se mantiene como una enfermedad altamente recurrente y son comunes los episodios repetidos. Finalmente, se conoce poco acerca de cómo puede ser prevenida la depresión, especialmente en sujetos con un alto riesgo. De cara a estos desafíos es que actualmente se están desarrollando varios excitantes esfuerzos de investigación que prometen expandir ampliamente nuestro conocimiento sobre la etiología, la fisiopatología y el tratamiento de la depresión. Esta revisión destaca estas perspectivas futuras para la investigación en la depresión, con un foco específico en las líneas de investigación que probablemente generarán nuevas y más efectivas opciones de tratamiento.

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