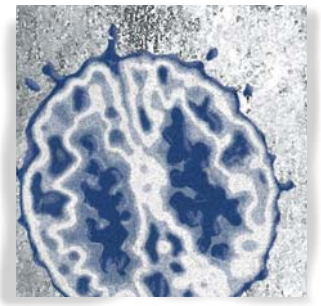
Future prospects in depression research

Paul E. Holtzheimer III, MD; Charles B. Nemeroff, MD, PhD



Major depression is a common, disabling, and often difficult-to-treat illness. Decades of research into the neurobiology and treatment of depression have greatly advanced our ability to manage this disorder. However, a number of challenges remain. A substantial number of depressed patients do not achieve full remission despite optimized treatment. For patients who do achieve resolution of symptoms, depression remains a highly recurrent illness, and repeated episodes are common. Finally, little is known about how depression might be prevented, especially in individuals at increased risk. In the face of these challenges, a number of exciting research efforts are currently under way and promise to greatly expand our knowledge of the etiology, pathophysiology, and treatment of depression. This review highlights these future prospects for depression research with a specific focus on lines of investigation likely to generate novel, more effective treatment options.

Dialogues Clin Neurosci. 2006;8:175-189.

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.[1] 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,[2] and depression is recognized to be one of the leading causes of disability worldwide.[3,4] 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.[5] However, up to 40% of patients continue to have clinically significant symptoms despite optimized treatment,[6] and up to 20% of patients may show little to no response to the most aggressive management (including the use of ECT).[7-9] 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.[10] Psychotherapy and/or maintenance antidepressant medications may substantially decrease the risk of relapse

Keywords: *depression; neuropsychopharmacology; neural network; neural stimulation*

Author affiliations: Emory University School of Medicine, Atlanta, Georgia, USA

Address for correspondence: Charles B. Nemeroff, Reunette W. Harris Professor and Chairman, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 101 Woodruff Circle, Suite 4000, Atlanta, Georgia 30322, USA
(e-mail: cnemero@emory.edu)

Selected abbreviations and acronyms

5-HT	*serotonin*
CNS	*central nervous system*
CRF	*corticotropin-releasing factor*
CSF	*cerebrospinal fluid*
DA	*dopamine*
DBS	*deep brain stimulation*
ECT	*electroconvulsive therapy*
GABA	*γ-aminobutyric acid*
HPA axis	*hypothalamic-pituitary-adrenal axis*
HPT axis	*hypothalamic-pituitary-thyroid axis*
NE	*norepinephrine*
SERT	*serotonin transporter*
SSRI	*selective serotonin reuptake inhibitor*
TMS	*transcranial magnetic stimulation*
VNS	*vagus nerve stimulation*

but do not eliminate it.[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,[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: $5\text{-HT}_{1a/b}$, $5\text{-HT}_{2a/c}$, and 5-HT_{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.[14] Cerebrospinal fluid (CSF) levels of serotonin metabolites—primarily 5-hydroxyindole acetic acid (5-HIAA)—are generally reduced in depressed patients[15] and are even lower in depressed patients with a history of suicide attempts.[16] Tryptophan depletion can lead to a depressive relapse in euthymic patients with a history of depression responsive to selective serotonin reuptake inhibitors (SSRIs).[17,18] SERT availability has been shown to be reduced in several brain regions in patients with major

depression,[19-21] though discordant findings have appeared.[22] Abnormalities in SERT binding have been consistently identified in depression.[23] 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-HT_2 receptors.[24] In unmedicated suicide victims with depression, an increased density of 5-HT_2 receptors has been reported in the prefrontal cortex and amygdala,[25] and, similar to findings with SERT, in platelets.[26] Treatment with antidepressant medications is generally associated with decreased density of 5-HT_2 receptors over a time course that corresponds to the onset of antidepressant efficacy—this finding suggests that upregulation of 5-HT_2 receptors in depression may be a compensatory response to a chronically low serotonergic state. However, other data suggest that 5-HT_2 receptor activity may not completely normalize with antidepressant treatment.[27] Also, using a radiolabled positron emission tomography (PET) ligand for the 5-HT_2 receptor, Biver et al[28] found reduced 5-HT_2 activity in the right orbitofrontal and insular cortices. Another group found no difference in 5-HT_2 activity in depressed patients versus normal controls[29]; 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)*.[30] 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.[31] A landmark study demonstrated that the *5-HTTLPR* polymorphism moderated the influence of stressful life events on the development of depression.[32] 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,[33,34] although not all studies are consistent.[35,36] Some studies have suggested this gene-environment interaction may be stronger in females than males.[35,37]

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.[38] Further, depleting NE (as well as DA) in euthymic, unmedicated patients with a history of depression can precipitate a relapse.[39] 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.[40] Drug-free depressed patients exhibit a blunted growth hormone response to clonidine, an α_2-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,[41,42] though this remains a controversial area. Chronic administration of antidepressant medications or electroconvulsive shock (ECS) are associated with increased noradrenergic neurotransmission.[43-48]

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[49]: (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,[50,51] and urine levels of 3,4-dihydroxyphenylacetic acid (DOPAC; another metabolite of DA) have been shown to be decreased in depressed patients[52] and potentially associated with suicidal behavior.[50] There is evidence from both brain imaging studies of the DAT[53] and postmortem studies[54] 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.[55-57] 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,[58-60] 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,[61] 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.[62,63] Studies exploring the interactions between the monoamine systems and other neurotransmitter/neuromodulatory systems (eg, CRF, neurokinins, 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.[64-66] 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 depresson.[67,68] Recently, we reported that NET polymorphisms predict response to milnacipran, a dual 5-HT/NE reuptake inhibitor, but not fluvoxamine, an SSRI.[69] 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.[70] Two main CRF receptor subtypes have been identified (CRF_1 and CRF_2) which appear to have differential effects on behaviors related to mood and anxiety. CRF_1 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, CRF_2 receptors have a lower affinity for CRF, have a widespread distribution with limited overlap with that of CRF_1 receptors, and reduced CRF_2 activity has been linked with *increased* anxiety-like behaviors in animals.[70,71]

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.[72,73] CRF concentrations are elevated in the frontal cortex of depressed patients, and there is a corresponding reduction in CRF_1 receptors in suicide victims in this area.[74,75] Further, antidepressants modify CRF activity. In a group of healthy volunteers, desipramine

was shown to decrease CSF CRF concentrations,[76] and both fluoxetine and ECT have been reported to produce similar changes in depressed patients.[77] 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).[78] Conversely, patients with nonpsychotic depression may demonstrate evidence of decreased or normal HPA axis activity.[79] 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.[80] 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.[81]

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_1 antagonists are in various stages of development (see Gutman et al[70] for a review). The effects of only one agent, R121919, have been published.[82] Although this agent showed evidence of antidepressant and anxiolytic activity in depressed patients,[82] 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, ketaconozale, aminoglutethimide, and metyrapone) have potential antidepressant effects; however, data are limited and the unfavorable side effects of these agents limit their potential utility.[83] The glucocorticoid receptor antagonist mifepristone (RU486)—a selective type II glucocorticoid receptor antagonist—has shown modest antidepressant effects in chronic depression,[84] and encouraging effects in the treatment of psychotic depression.[85,86] 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.[87]

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,[88,89] though discordant findings have been reported.[90] Several studies have revealed a

blunted TSH response to TRH stimulation in depressed patients despite normal thyroid hormone levels,[91] 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.[92,93] Thyroid hormone augmentation (primarily with T_3) has been reported to exert antidepressant effects, even in the absence of clinical hypothyroidism,[94-95] though several negative studies are available (P. Ninan and C. B. Nemeroff, unpublished observations).[96]

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 MT_1/MT_2 receptors and an antagonist at $5HT_{2c}$ receptors, has proven its antidepressant efficacy in clinical trials,[97] 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-isoxazide propionic acid [AMPA], and kainite receptors) and metabotropic (including a family of G-protein coupled receptors associated with adenyl cyclase and phosphoinositide second messenger systems). Excitatory glutamatergic neurotransmission likely plays a role in depression.[98,99] 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.[100]

Ionotropic glutamate receptor antagonists can decrease stress-induced loss of hippocampal neurons,[101,102] and data suggest amantadine (a nonselective NMDA receptor antagonist) may enhance antidepressant-like effects of typical antidepressants in animal models[103,104] and depressed patients.[105] Preclinical studies of selective NMDA receptor antagonists have revealed antidepressant-like effects in animal models.[106,107] Additionally, agents that enhance AMPA receptor function may augment antidepressant effects of standard antidepressant medications.[108] Riluzole, which inhibits glutamate release, has shown preliminary antidepressant effects in patients with bipolar depression,[109,110] 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.[111,112] Preclinical studies have demonstrated decreased CNS GABA concentrations in animal models of depression.[111] CSF and plasma GABA concentrations have been reported to be decreased in depressed patients.[111] Postmortem investigation of the hippocampus in depressed patients suggested possible GABAergic dysfunction.[113] $GABA_b$ 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.[114] Modulating $GABA_b$ function has been shown to have important behavioral effects in animal models, with $GABA_b$ antagonists demonstrating certain antidepressant-like properties.[112,114] Using magnetic resonance spectroscopy, Sanacora et al demonstrated decreased GABA concentrations in the occipital cortex of depressed patients.[100,115] Moreover, this group showed GABA concentrations increase in the occipital cortex after SSRI treatment and ECT,[116,117] but not after CBT.[118] CNS GABA concentrations have also been shown to be normal in remitted depressed patients compared with controls.[119]

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.[120] Substance P is also colocalized in cells containing 5-HT and NE.[121-124] 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 characteristics of a stress response.[125,126] These changes can be attenuated by substance P antagonists.[127,128] Supporting its role in depression, CSF substance P concentrations were reported to be elevated in depressed patients compared with controls,[129-131] and lower serum concentrations of substance P have been correlated with better antidepressant treatment response.[130] Our group has reported elevations in CSF substance P concentrations in drug-free patients with major depression and PTSD.[132] One placebo-controlled study using a neurokinin receptor (NK-1) antagonist (MK-869) suggested efficacy in treating depression,[127] but several follow-up studies found no significant antidepressant effects for this agent.[133] Two other selective NK-1 receptor antagonists (L-759274 and CP-122721) have shown potential efficacy in treating depression,[134,135] 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,[136-141] 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.[140,142]

As data have accumulated, increasingly complex models of mood regulation have been developed.[136,137,139,143,144] 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[145]; 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,[146] 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,[147,148] and functional imaging studies have confirmed that TMS can modulate function in several brain regions (including subcortical structures) implicated in mood regulation.[149,150] Several studies have shown antidepressant effects for fast rTMS applied to the left dorsolateral prefrontal cortex[151,152]; a smaller number have shown efficacy for slow rTMS applied to the right dorsolateral prefrontal cortex.[153,154] 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.[155] 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,[156,157] 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.[158] 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.[159] Combined with neurochemical imaging (such as receptor imaging), TMS can be used to probe the role of specific neurotransmitter systems.[150]

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[160] and was recently approved for the adjunctive treatment of a major depressive episode that has not responded to at least four antidepressant medication trials. However, the efficacy data on VNS are mixed. Mood improvements have been reported by epileptic patients receiving VNS,[161] and one open and one double-blind study have shown antidepressant efficacy for VNS in depressed epilepsy patients.[162,163] 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[164]; response and remission were generally maintained after at least 1 year of treatment[165] and showed further increases after 2 years of treatment.[166] However, a large, sham-controlled study failed to show statistically significant antidepressant effects for active VNS[167] 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%.[168] 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).[169] 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 pharmaco-resistant 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.[170] VNS may affect function of GABA,[171,172] DA,[173] and NE,[174-177] though conflicting data have been reported.[173] These neurotransmitter system effects have not been consistently associated with therapeutic response.[171]

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,[178,179] and can be associated with significant mood changes in patients with Parkinson's disease.[180,181] 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).[182] 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).[182] DBS appears to modulate function within discrete neural networks,[183] 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. ❑

ACKNOWLEDGEMENTS

This work was supported by the NIH/National Institute of Mental Health (MH 58922, MH 42088 and MH 69056) (CBN) and by the Emory Mentored Clinical Research Scholars Program through a grant from NIH/National Center for Research Resources (RR 17643) (PEH).

DISCLOSURES

CBN has received grants from the American Foundation for Suicide Prevention (AFSP), AstraZeneca, Bristol-Myers-Squibb, Forest Laboratories, Janssen Pharmaceutica, National Alliance for Research in Schizophrenia and Depression (NARSAD), National Institute of Mental Health (NIMH), Pfizer Pharmaceuticals, and Wyeth-Ayerst. He is a consultant for Abbott Laboratories, Acadia Pharmaceuticals, Bristol-Myers-Squibb, Corcept, Cypress Biosciences, Cyberonics, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceutica, Otsuka, Pfizer Pharmaceuticals, and Quintiles. He is on the Speakers Bureau for Abbott Laboratories, GlaxoSmithKline, Janssen Pharmaceutica, and Pfizer Pharmaceuticals. He owns stock in Corcept, Cypress Biosciences and Acadia Pharmaceuticals. He is on the Board of Directors for AFSP, American Psychiatric Institute for Research and Education (APIRE), George West Mental Health Foundation, Novadel Pharma, National Foundation for Mental Health (NFMH). He has patents for "Method and devices for transdermal delivery of lithium (US 6,375,990 B1)" and "Method to estimate serotonin and norepinephrine transporter occupancy after drug treatment using patient or animal serum (provisional filing April, 2001)." He has equity in Reevax, BMC-JR LLC, and CeNeRx.

PEH has received grants from the American Federation for Aging Research (AFAR), Neuronetics, Inc, and the National Center for Research Resources.

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.

Perspectives dans la recherche sur la dépression

La dépression majeure est une maladie répandue, invalidante et souvent difficile à traiter. Des décennies de recherche en neurobiologie et dans le traitement de la dépression nous ont fait beaucoup avancer dans la prise en charge de ce trouble. Il persiste néanmoins quelques défis à relever. Un nombre non négligeable de patients déprimés bénéficiant pourtant d'un traitement optimal, ne guérissent pas complètement. Pour les patients dont les symptômes disparaissent, la dépression demeure à haut risque de récidive et les épisodes répétés sont fréquents. En fin de compte, nous en savons peu sur la prévention de la dépression surtout chez les sujets dont le risque est augmenté. En réponse à ces questions, des efforts de recherche passionnants sont actuellement en cours et vont permettre d'enrichir notre connaissance de l'étiologie, de la physiopathologie et du traitement de la dépression. Cette mise au point met en lumière ces perspectives pour la recherche sur la dépression avec un intérêt particulier pour les voies qui déboucheront probablement sur de nouvelles possibilités thérapeutiques, plus efficaces.

REFERENCES

1. Rush AJ, Fava M, Wisniewski SR, et al. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Control Clin Trials*. 2004;25:119-142.
2. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62:593-602.
3. Murray CJL, Lopez AD, eds. *The Global Burden of Disease*. Boston, Mass: Harvard University Press; 1996.
4. The WHO World Mental Health Survey Consortium. Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. *JAMA*. 2004;291:2581-2590.
5. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med*. 2000;342:1462-1470.
6. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry*. 2003;53:649-659.
7. Keller MB, Lavori PW, Mueller TI, et al. Time to recovery, chronicity, and levels of psychopathology in major depression. A 5-year prospective follow-up of 431 subjects. *Arch Gen Psychiatry*. 1992;49:809-816.
8. Fink M. Convulsive therapy: a review of the first 55 years. *J Affect Disord*. 2001;63:1-15.
9. Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry*. 2001;62(suppl 16):10-17.
10. Kennedy S, McIntyre R, Fallu A, Lam R. Pharmacotherapy to sustain the fully remitted state. *J Psychiatry Neurosci*. 2002;27:269-280.
11. Thase ME. Achieving remission and managing relapse in depression. *J Clin Psychiatry*. 2003;64(suppl)18:3-7.
12. Prange AJ Jr. The pharmacology and biochemistry of depression. *Dis Nerv Syst*. 64;25:217-221.
13. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry*. 1965;122:509-522.
14. Risch SC, Nemeroff CB. Neurochemical alterations of serotonergic neuronal systems in depression. *J Clin Psychiatry*. 1992;53(suppl):3-7.
15. Asberg M, Thoren P, Traskman L, Bertilsson L, Ringberger V. "Serotonin depression"- a biochemical subgroup within the affective disorders? *Science*. 1976;191:478-480.

16. Mann JJ, Malone KM, Psych MR, et al. Attempted suicide characteristics and cerebrospinal fluid amine metabolites in depressed inpatients. *Neuropsychopharmacology*. 1996;15:576-586.
17. Smith KA, Fairburn CG, Cowen PJ. Relapse of depression after rapid depletion of tryptophan. *Lancet*. 1997;349:915-919.
18. Booij L, Van der Does W, Benkelfat C, et al. Predictors of mood response to acute tryptophan depletion. A reanalysis. *Neuropsychopharmacology*. 2002;27:852-861.
19. Malison RT, Price LH, Berman R, van Dyck CH, et al. Reduced brain serotonin transporter availability in major depression as measured by [123I]-2 beta-carbomethoxy-3 beta-(4-iodophenyl)tropane and single photon emission computed tomography. *Biol Psychiatry*. 1998;44:1090-1098.
20. Perry EK, Marshall EF, Blessed G, Tomlinson BE, Perry RH. Decreased imipramine binding in the brains of patients with depressive illness. *Br J Psychiatry*. 1983;142:188-192.
21. Stanley M, Virgilio J, Gershon S. Tritiated imipramine binding sites are decreased in the frontal cortex of suicides. *Science*. 1982;216:1337-1339.
22. Little KY, McLauglin DP, Ranc J, et al. Serotonin transporter binding sites and mRNA levels in depressed persons committing suicide. *Biol Psychiatry*. 1997;41:1156-1164.
23. Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin Chem*. 1994;40:288-295.
24. Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors. Serotonin receptors and pathways mediate therapeutic effects and side effects. *J Affect Disord*. 1998;51:215-235.
25. Hrdina PD, Demeter E, Vu TB, Sotonyi P, Palkovits M. 5-HT uptake sites and 5-HT2 receptors in brain of antidepressant-free suicide victims/depressives: increase in 5-HT2 sites in cortex and amygdala. *Brain Res*. 1993;614:37-44.
26. Biegon A, Weizman A, Karp L, Ram A, Tiano S, Wolff M. Serotonin 5-HT2 receptor binding on blood platelets—a peripheral marker for depression? *Life Sci*. 1987;41:2485-2492.
27. Bakish D, Cavazzoni P, Chudzik J, Ravindran A, Hrdina PD. Effects of selective serotonin reuptake inhibitors on platelet serotonin parameters in major depressive disorder. *Biol Psychiatry*. 1997;41:184-190.
28. Biver F, Wikler D, Lotstra F, Damhaut P, Goldman S, Mendlewicz J. Serotonin 5-HT2 receptor imaging in major depression: focal changes in orbito-insular cortex. *Br J Psychiatry*. 1997;171:444-448.
29. Meyer JH, Kapur S, Houle S, et al. Prefrontal cortex 5-HT2 receptors in depression: an [18F]setoperone PET imaging study. *Am J Psychiatry*. 1999;156:1029-1034.
30. Mann JJ, Huang YY, Underwood MD, et al. A serotonin transporter gene promoter polymorphism (5-HTTLPR) and prefrontal cortical binding in major depression and suicide. *Arch Gen Psychiatry*. 2000;57:729-738.
31. Sen S, Burmeister M, Ghosh D. Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. *Am J Med Genet B Neuropsychiatr Genet*. 2004;127:85-89.
32. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301:386-389.
33. Kendler KS, Kuhn JW, Vittum J, Prescott CA, Riley B. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. *Arch Gen Psychiatry*. 2005;62:529-535.
34. Kaufman J, Yang BZ, Douglas-Palumberi H, et al. Social supports and serotonin transporter gene moderate depression in maltreated children. *Proc Natl Acad Sci U S A*. 2004;101:17316-17321.
35. Grabe HJ, Lange M, Wolff B, et al. Mental and physical distress is modulated by a polymorphism in the 5-HT transporter gene interacting with social stressors and chronic disease burden. *Mol Psychiatry*. 2005;10:220-224.
36. Gillespie NA, Whitfield JB, Williams B, Heath AC, Martin NG. The relationship between stressful life events, the serotonin transporter (5-HTTLPR) genotype and major depression. *Psychol Med*. 2005;35:101-111.
37. Eley TC, Sugden K, Corsico A, et al. Gene-environment interaction analysis of serotonin system markers with adolescent depression. *Mol Psychiatry*. 2004;9:908-915.
38. Charney DS. Monoamine dysfunction and the pathophysiology and treatment of depression. *J Clin Psychiatry*. 1998;59(suppl 14):11-14.
39. Berman RM, Narasimhan M, Miller HL, et al Transient depressive relapse induced by catecholamine depletion: potential phenotypic vulnerability marker? *Arch Gen Psychiatry*. 1999;56:395-403.
40. Ordway GA. Pathophysiology of the locus coeruleus in suicide. *Ann N Y Acad Sci.* 1997;836:233-252.
41. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry*. 2001;178:234-241.
42. Hansen RA, Gartlehner G, Lohr KN, Gaynes BN, Carey TS. Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. *Ann Intern Med*. 20 2005;143:415-426.
43. Deakin JF, Owen F, Cross AJ, Dashwood MJ. Studies on possible mechanisms of action of electroconvulsive therapy; effects of repeated electrically induced seizures on rat brain receptors for monoamines and other neurotransmitters. *Psychopharmacology (Berl)*. 1981;73:345-349.
44. Pandey GN, Sudershan P, Davis JM. Beta adrenergic receptor function in depression and the effect of antidepressant drugs. *Acta Pharmacol Toxicol (Copenh).* 1985;56(suppl 1):66-79.
45. Nimgaonkar VL, Goodwin GM, Davies CL, Green AR. Down-regulation of beta-adrenoceptors in rat cortex by repeated administration of desipramine, electroconvulsive shock and clenbuterol requires 5-HT neurones but not 5-HT. *Neuropharmacology*. 85;24:279-283.
46. Heal DJ, Prow MR, Buckett WR. Effects of antidepressant drugs and electroconvulsive shock on pre- and postsynaptic alpha 2-adrenoceptor function in the brain: rapid down-regulation by sibutramine hydrochloride. *Psychopharmacology (Berl).* 1991;103:251-257.
47. Nalepa I, Vetulani J. Different mechanisms of beta-adrenoceptor down-regulation by chronic imipramine and electroconvulsive treatment: possible role for protein kinase C. *J Neurochem*. 1991;57:904-910.
48. Mann JJ, Mahler JC, Wilner PJ, et al. Normalization of blunted lymphocyte beta-adrenergic responsivity in melancholic inpatients by a course of electroconvulsive therapy. *Arch Gen Psychiatry*. 1990;47:461-464.
49. Moore RY, Bloom FE. Central catecholamine neuron systems: anatomy and physiology of the dopamine systems. *Annu Rev Neurosci*. 1978;1:129-169.
50. Roy A, Karoum F, Pollack S. Marked reduction in indexes of dopamine metabolism among patients with depression who attempt suicide. *Arch Gen Psychiatry.* 1992;49:447-450.
51. Reddy PL, Khanna S, Subhash MN, Channabasavanna SM, Rao BS. CSF amine metabolites in depression. *Biol Psychiatry*. 1992;31:112-118.
52. Roy A, Pickar D, Douillet P, Karoum F, Linnoila M. Urinary monoamines and monoamine metabolites in subtypes of unipolar depressive disorder and normal controls. *Psychol Med*. 1986;16:541-546.
53. Meyer JH, Kruger S, Wilson AA, et al. Lower dopamine transporter binding potential in striatum during depression. *Neuroreport*. 2001;12:4121-4125.
54. Klimek V, Schenck JE, Han H, Stockmeier CA, Ordway GA. Dopaminergic abnormalities in amygdaloid nuclei in major depression: a postmortem study. *Biol Psychiatry*. 2002;52:740-748.
55. D'Amato RJ, Zweig RM, Whitehouse PJ, et al. Aminergic systems in Alzheimer's disease and Parkinson's disease. *Ann Neurol*. 1987;22:229-236.
56. Remy P, Doder M, Lees A, Turjanski N, Brooks D. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain*. 16 2005;128:1314-1322.
57. Chan-Palay V, Asan E. Alterations in catecholamine neurons of the locus coeruleus in senile dementia of the Alzheimer type and in Parkinson's disease with and without dementia and depression. *J Comp Neurol*. 1989;287:373-392.
58. Nierenberg AA, Dougherty D, Rosenbaum JF. Dopaminergic agents and stimulants as antidepressant augmentation strategies. *J Clin Psychiatry*. 1998;59(suppl 5):60-63; discussion 64.
59. Zarate CA, Jr, Payne JL, Singh J, et al. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biol Psychiatry*. 2004;56:54-60.
60. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry*. 2004;161:564-566.

61. Santarelli L, Saxe M, Gross C, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science*. 2003;301:805-809.
62. Skolnick P, Popik P, Janowsky A, Beer B, Lippa AS. Antidepressant-like actions of DOV 21,947: a "triple" reuptake inhibitor. *Eur J Pharmacol*. 2003;461:99-104.
63. Skolnick P, Popik P, Janowsky A, Beer B, Lippa AS. "Broad spectrum" antidepressants: is more better for the treatment of depression? *Life Sci*. 2003;73:3175-3179.
64. Neumeister A, Nugent AC, Waldeck T, et al. Neural and behavioral responses to tryptophan depletion in unmedicated patients with remitted major depressive disorder and controls. *Arch Gen Psychiatry*. 2004;61:765-773.
65. Bremner JD, Innis RB, Salomon RM, et al. Positron emission tomography measurement of cerebral metabolic correlates of tryptophan depletion-induced depressive relapse. *Arch Gen Psychiatry*. 1997;54:364-374.
66. Bremner JD, Vythilingam M, Ng CK, et al. Regional brain metabolic correlates of alpha-methylparatyrosine-induced depressive symptoms: implications for the neural circuitry of depression. *JAMA*. 2003;289:3125-3134.
67. Pezawas L, Meyer-Lindenberg A, Drabant EM, et al. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. *Nat Neurosci*. 2005;8:828-834.
68. Graff-Guerrero A, De la Fuente-Sandoval C, Camarena B, et al. Frontal and limbic metabolic differences in subjects selected according to genetic variation of the SLC6A4 gene polymorphism. *Neuroimage*. 2005;25:1197-1204.
69. Yoshida K, Takahashi H, Higuchi H, et al. Prediction of antidepressant response to milnacipran by norepinephrine transporter gene polymorphisms. *Am J Psychiatry*. 2004;161:1575-1580.
70. Gutman DA, Owens MJ, Nemeroff CB. Corticotropin-releasing factor receptor and glucocorticoid receptor antagonists: new approaches to antidepressant treatment. In: Den Boer JA, George MS, ter Horst GJ, eds. *Current and Future Developments in Psychopharmacology*. Amsterdam, the Netherlands: Benecke, NI; 2005.
71. Skelton KH, Nemeroff CB, Owens MJ. Spontaneous withdrawal from the triazolobenzodiazepine alprazolam increases cortical corticotropin-releasing factor mRNA expression. *J Neurosci*. 2004;24:9303-9312.
72. Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB. The role of corticotropin-releasing factor in depression and anxiety disorders. *J Endocrinol*. 1999;160:1-12.
73. Raadsheer FC, Hoogendijk WJ, Stam FC, Tilders FJ, Swaab DF. Increased numbers of corticotropin-releasing hormone expressing neurons in the hypothalamic paraventricular nucleus of depressed patients. *Neuroendocrinology*. 1994;60:436-444.
74. Nemeroff CB, Owens MJ, Bissette G, Andorn AC, Stanley M. Reduced corticotropin releasing factor binding sites in the frontal cortex of suicide victims. *Arch Gen Psychiatry*. 1988;45:577-579.
75. Merali Z, Du L, Hrdina P, Palkovits M, Faludi G, Poulter MO, Anisman H. Dysregulation in the suicide brain: mRNA expression of corticotropin-releasing hormone receptors and GABA(A) receptor subunits in frontal cortical brain region. *J Neurosci*. 2004;24:1478-1485.
76. Veith RC, Lewis N, Langohr JI, et al. Effect of desipramine on cerebrospinal fluid concentrations of corticotropin-releasing factor in human subjects. *Psychiatry Res*. 1993;46:1-8.
77. Nemeroff CB, Bissette G, Akil H, Fink M. Neuropeptide concentrations in the cerebrospinal fluid of depressed patients treated with electroconvulsive therapy. Corticotrophin-releasing factor, beta-endorphin and somatostatin. *Br J Psychiatry*. 1991;158:59-63.
78. Schatzberg AF, Rothschild AJ, Stahl JB, et al. The dexamethasone suppression test: identification of subtypes of depression. *Am J Psychiatry*. 1983;140:88-91.
79. Posener JA, DeBattista C, Williams GH, Chmura Kraemer H, Kalehzan BM, Schatzberg AF. 24-Hour monitoring of cortisol and corticotropin secretion in psychotic and nonpsychotic major depression. *Arch Gen Psychiatry*. 2000;57:755-760.
80. Heim C, Newport DJ, Heit S, et al. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA*. 2000;284:592-597.
81. Nemeroff CB, Heim CM, Thase ME, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proc Natl Acad Sci U S A*. 2003;100:14293-14296.
82. Zobel AW, Nickel T, Kunzel HE, Ackl N, Sonntag A, Ising M, Holsboer F. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J Psychiatr Res*. 2000;34:171-181.
83. Wolkowitz OM, Reus VI. Treatment of depression with antiglucocorticoid drugs. *Psychosom Med.* 1999;61:698-711.
84. Murphy BE, Filipini D, Ghadirian AM. Possible use of glucocorticoid receptor antagonists in the treatment of major depression: preliminary results using RU 486. *J Psychiatry Neurosci*. 1993;18:209-213.
85. Belanoff JK, Flores BH, Kalezhan M, Sund B, Schatzberg AF. Rapid reversal of psychotic depression using mifepristone. *J Clin Psychopharmacol*. 2001;21:516-521.
86. Belanoff JK, Rothschild AJ, Cassidy F, et al. An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biol Psychiatry*. 2002;52:386-392.
87. Tyrka AR, Carpenter LL, McDougle CJ, et al. Increased cerebrospinal fluid corticotropin-releasing factor concentrations during tryptophan depletion in healthy adults. *Biol Psychiatry*. 2004;56:531-534.
88. Banki CM, Bissette G, Arato M, Nemeroff CB. Elevation of immunoreactive CSF TRH in depressed patients. *Am J Psychiatry*. 1988;145:1526-1531.
89. Kirkegaard C, Faber J, Hummer L, Rogowski P. Increased levels of TRH in cerebrospinal fluid from patients with endogenous depression. *Psychoneuroendocrinology*. 1979;4:227-235.
90. Roy A, Wolkowitz OM, Bissette G, Nemeroff CB. Differences in CSF concentrations of thyrotropin-releasing hormone in depressed patients and normal subjects: negative findings. *Am J Psychiatry*. 94;151:600-602.
91. Esposito S, Prange AJ, Jr, Golden RN. The thyroid axis and mood disorders: overview and future prospects. *Psychopharmacol Bull*. 1997;33:205-217.
92. Sullivan GM, Hatterer JA, Herbert J, et al. Low levels of transthyretin in the CSF of depressed patients. *Am J Psychiatry*. 1999;156:710-715.
93. Hatterer JA, Herbert J, Hidaka C, Roose SP, Gorman JM. CSF transthyretin in patients with depression. *Am J Psychiatry*. 1993;150:813-815.
94. Aronson R, Offman HJ, Joffe RT, Naylor CD. Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. *Arch Gen Psychiatry*. 1996;53:842-848.
95. Iosifescu DV, Nierenberg AA, Mischoulon D, et al. An open study of triiodothyronine augmentation of selective serotonin reuptake inhibitors in treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2005;66:1038-1042.
96. Appelhof BC, Brouwer JP, van Dyck R, et al. Triiodothyronine addition to paroxetine in the treatment of major depressive disorder. *J Clin Endocrinol Metab*. 2004;89:6271-6276.
97. Kennedy SH, Emsley R. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. *Eur Neuropsychopharmacol*. 2006;16:93-100.
98. Paul IA, Skolnick P. Glutamate and depression: clinical and preclinical studies. *Ann N Y Acad Sci*. 2003;1003:250-272.
99. Zarate CA, Jr., Du J, Quiroz J, et al. Regulation of cellular plasticity cascades in the pathophysiology and treatment of mood disorders: role of the glutamatergic system. *Ann N Y Acad Sci*. 2003;1003:273-291.
100. Sanacora G, Gueorguieva R, Epperson CN, et al. Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. *Arch Gen Psychiatry*. 2004;61:705-713.
101. McEwen BS. Stress and hippocampal plasticity. *Annu Rev Neurosci*. 1999;22:105-122.
102. Sapolsky RM. The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. *Biol Psychiatry*. 2000;48:755-765.
103. Rogoz Z, Skuza G, Maj J, Danysz W. Synergistic effect of uncompetitive NMDA receptor antagonists and antidepressant drugs in the forced swimming test in rats. *Neuropharmacology*. 2002;42:1024-1030.
104. Rogoz Z, Skuza G, Kusmider M, Wojcikowski J, Kot M, Daniel WA. Synergistic effect of imipramine and amantadine in the forced swimming test in rats. Behavioral and pharmacokinetic studies. *Pol J Pharmacol*. 2004;56:179-185.

105. Stryjer R, Strous RD, Shaked G, et al. Amantadine as augmentation therapy in the management of treatment-resistant depression. *Int Clin Psychopharmacol*. 2003;18:93-96.
106. Palucha A, Branski P, Szewczyk B, Wieronska JM, Klak K, Pilc A. Potential antidepressant-like effect of MTEP, a potent and highly selective mGluR5 antagonist. *Pharmacol Biochem Behav*. 2005;81:901-906.
107. Pilc A, Klodzinska A, Branski P, et al. Multiple MPEP administrations evoke anxiolytic- and antidepressant-like effects in rats. *Neuropharmacology*. 2002;43:181-187.
108. Li X, Witkin JM, Need AB, Skolnick P. Enhancement of antidepressant potency by a potentiator of AMPA receptors. *Cell Mol Neurobiol*. 2003;23:419-430.
109. Zarate CA, Jr, Payne JL, Quiroz J, et al. An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry*. 2004;161:171-174.
110. Zarate CA, Jr., Quiroz JA, Singh JB, et al. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. *Biol Psychiatry*. 15 2005;57:430-432.
111. Brambilla P, Perez J, Barale F, Schettini G, Soares JC. GABAergic dysfunction in mood disorders. *Mol Psychiatry*. 2003;8:721-737, 715.
112. Krystal JH, Sanacora G, Blumberg H, et al. Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. *Mol Psychiatry*. 2002;7(suppl 1):S71-80.
113. Knable MB, Barci BM, Webster MJ, Meador-Woodruff J, Torrey EF. Molecular abnormalities of the hippocampus in severe psychiatric illness: postmortem findings from the Stanley Neuropathology Consortium. *Mol Psychiatry*. 2004;6:6.
114. Cryan JF, Kaupmann K. Don't worry 'B' happy!: a role for GABA(B) receptors in anxiety and depression. *Trends Pharmacol Sci*. 2005;26:36-43.
115. Sanacora G, Mason GF, Rothman DL, et al. Reduced cortical gamma-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. *Arch Gen Psychiatry*. 1999;56:1043-1047.
116. Sanacora G, Mason GF, Rothman DL, Krystal JH. Increased occipital cortex GABA concentrations in depressed patients after therapy with selective serotonin reuptake inhibitors. *Am J Psychiatry*. 2002;159:663-665.
117. Sanacora G, Mason GF, Rothman DL, et al. Increased cortical GABA concentrations in depressed patients receiving ECT. *Am J Psychiatry*. 2003;160:577-579.
118. Sanacora G, Fenton LR, Fasula MK, et al. Cortical gamma-aminobutyric acid concentrations in depressed patients receiving cognitive behavioral therapy. *Biol Psychiatry*. 2006;59:40-47.
119. Hasler G, Neumeister A, van der Veen JW, et al. Normal prefrontal gamma-aminobutyric acid levels in remitted depressed subjects determined by proton magnetic resonance spectroscopy. *Biol Psychiatry*. 2005;58:969-973.
120. Ku YH, Tan L, Li LS, Ding X. Role of corticotropin-releasing factor and substance P in pressor responses of nuclei controlling emotion and stress. *Peptides*. 1998;19:677-682.
121. Bittencourt JC, Benoit R, Sawchenko PE. Distribution and origins of substance P-immunoreactive projections to the paraventricular and supraoptic nuclei: partial overlap with ascending catecholaminergic projections. *J Chem Neuroanat*. 1991;4:63-78.
122. Magoul R, Dubourg P, Benjelloun W, Tramu G. Synaptic inputs of tachykinin-containing nerve terminals to target tyrosine-hydroxylase-, beta-endorphin- and neuropeptide Y-producing neurons of the arcuate nucleus. Double pre-embedding immunocytochemical study in the rat. *J Chem Neuroanat*. 1993;6:419-429.
123. Pelletier G, Steinbusch HW, Verhofstad AA. Immunoreactive substance P and serotonin present in the same dense-core vesicles. *Nature*. 1981;293:71-72.
124. Helke CJ, Yang L. Interactions and coexistence of neuropeptides and serotonin in spinal autonomic systems. *Ann N Y Acad Sci*. 1996;780:185-192.
125. Culman J, Unger T. Central tachykinins: mediators of defence reaction and stress reactions. *Can J Physiol Pharmacol*. 1995;73:885-891.
126. Helke CJ, Krause JE, Mantyh PW, Couture R, Bannon MJ. Diversity in mammalian tachykinin peptidergic neurons: multiple peptides, receptors, and regulatory mechanisms. *Faseb J*. 1990;4:1606-1615.
127. Kramer MS, Cutler N, Feighner J, et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science*. 1998;281:1640-1645.
128. Culman J, Klee S, Ohlendorf C, Unger T. Effect of tachykinin receptor inhibition in the brain on cardiovascular and behavioral responses to stress. *J Pharmacol Exp Ther*. 1997;280:238-246.
129. Rimon R, Le Greves P, Nyberg F, Heikkila L, Salmela L, Terenius L. Elevation of substance P-like peptides in the CSF of psychiatric patients. *Biol Psychiatry*. 1984;19:509-516.
130. Bondy B, Baghai TC, Minov C, et al. Substance P serum levels are increased in major depression: preliminary results. *Biol Psychiatry*. 2003;53:538-542.
131. Berrettini WH, Rubinow DR, Nurnberger JI, Jr, Simmons-Alling S, Post RM, Gershon ES. CSF substance P immunoreactivity in affective disorders. *Biol Psychiatry*. 1985;20:965-970.
132. Geracioti TD, Carpenter L, Owens MJ, et al. Elevated cerebrospinal fluid substance P concentrations in post-traumatic stress disorder and major depression. *Am J Psychiatry*. 2006. In press.
133. Krishnan KR. Clinical experience with substance P receptor (NK1) antagonists in depression. *J Clin Psychiatry*. 2002;63(suppl 11):25-29.
134. Kramer MS, Winokur A, Kelsey J, et al. Demonstration of the efficacy and safety of a novel substance P (NK1) receptor antagonist in major depression. *Neuropsychopharmacology*. 2004;29:385-392.
135. Herpfer I, Lieb K. Substance P receptor antagonists in psychiatry: rationale for development and therapeutic potential. *CNS Drugs*. 2005;19:275-293.
136. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry.* 2003;54:504-514.
137. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol Psychiatry*. 2003;54:515-528.
138. Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Curr Opin Neurobiol*. 2001;11:240-249.
139. Mayberg HS. Positron emission tomography imaging in depression: a neural systems perspective. *Neuroimaging Clin N Am*. 2003;13:805-815.
140. Harrison PJ. The neuropathology of primary mood disorder. *Brain*. 2002;125:1428-1449.
141. Robinson RG, Chemerinski E, Jorge R. Pathophysiology of secondary depressions in the elderly. *J Geriatr Psychiatry Neurol*. 1999;12:128-136.
142. Taylor WD, MacFall JR, Payne ME, et al. Late-life depression and microstructural abnormalities in dorsolateral prefrontal cortex white matter. *Am J Psychiatry*. 2004;161:1293-1296.
143. Drevets WC, Raichle ME. Neuroanatomical circuits in depression: implications for treatment mechanisms. *Psychopharmacol Bull*. 1992;28:261-274.
144. Rauch SL. Neuroimaging and neurocircuitry models pertaining to the neurosurgical treatment of psychiatric disorders. *Neurosurg Clin N Am*. 2003;14:213-223, vii-viii. Review.
145. Ramnani N, Behrens TE, Penny W, Matthews PM. New approaches for exploring anatomical and functional connectivity in the human brain. *Biol Psychiatry*. 2004;56:613-619.
146. Anand S, Hotson J. Transcranial magnetic stimulation: Neurophysiological applications and safety. *Brain Cogn*. 2002;50:366-386.
147. Fleischmann A, Prolov K, Abarbanel J, Belmaker RH. The effect of transcranial magnetic stimulation of rat brain on behavioral models of depression. *Brain Res*. 1995;699:130-132.
148. Post RM, Kimbrell TA, McCann UD, et al. Repetitive transcranial magnetic stimulation as a neuropsychiatric tool: present status and future potential. *J ECT*. 1999;15:39-59.
149. Kimbrell TA, Little JT, Dunn RT, et al. Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. *Biol Psychiatry*. 1999;46:1603-1613.
150. Strafella AP, Paus T, Fraraccio M, Dagher A. Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. *Brain*. 2003;22:22.
151. Holtzheimer PE 3rd, Russo J, Avery DH. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. *Psychopharmacol Bull*. 2001;35:149-169. Erratum in: *Psychopharmacol Bull*. 2003;2037:2005.

152. Martin JL, Barbanoj MJ, Schlaepfer TE, Thompson E, Perez V, Kulisevsky J. Repetitive transcranial magnetic stimulation for the treatment of depression: Systematic review and meta-analysis. *Br J Psychiatry*. 2003;182:480-491.
153. Klein E, Kreinin I, Chistyakov A, et al Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. *Arch Gen Psychiatry*. 1999;56:315-320.
154. Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, De Castella A, Kulkarni J. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 2003;60:1002-1008.
155. Schlaepfer TE, Kosel M, Nemeroff CB. Efficacy of repetitive transcranial magnetic stimulation (rTMS) in the treatment of affective disorders. *Neuropsychopharmacology*. 2003;28:201-205.
156. Lisanby SH, Luber B, Schlaepfer TE, Sackeim HA. Safety and feasibility of magnetic seizure therapy (MST) in major depression: randomized within-subject comparison with electroconvulsive therapy. *Neuropsychopharmacology*. 2003;28:1852-1865.
157. Kosel M, Frick C, Lisanby SH, Fisch HU, Schlaepfer TE. Magnetic seizure therapy improves mood in refractory major depression. *Neuropsychopharmacology*. 2003;28:2045-2048.
158. Paus T. Imaging the brain before, during, and after transcranial magnetic stimulation. *Neuropsychologia*. 1999;37:219-224.
159. Paus T, Barrett J. Transcranial magnetic stimulation (TMS) of the human frontal cortex: implications for repetitive TMS treatment of depression. *J Psychiatry Neurosci*. 2004;29:268-279.
160. Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. *Lancet Neurol*. 2002;1:477-482.
161. George MS, Rush AJ, Sackeim HA, Marangell LB. Vagus nerve stimulation (VNS): utility in neuropsychiatric disorders. *Int J Neuropsychopharmacol*. 2003;6:73-83.
162. Harden CL, Pulver MC, Ravdin LD, Nikolov B, Halper JP, Labar DR. A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. *Epilepsy Behav*. 2000;1:93-99.
163. Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. *Epilepsy Res*. 2000;42:203-210.
164. Sackeim HA, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology*. 2001;25:713-728.
165. Marangell LB, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. *Biol Psychiatry*. 2002;51:280-287.
166. Nahas Z, Marangell LB, Husain MM. Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. *J Clin Psychiatry*. 2005;66:1097-1104.
167. Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol Psychiatry*. 2005;58:347-354.
168. Rush AJ, Sackeim HA, Marangell LB, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. *Biol Psychiatry*. 2005;58:355-363.
169. George MS, Rush AJ, Marangell LB, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry*. 2005;58:364-373.
170. Chae JH, Nahas Z, Lomarev M, et al. A review of functional neuroimaging studies of vagus nerve stimulation (VNS). *J Psychiatr Res*. 2003;37:443-455.
171. Ben-Menachem E, Hamberger A, Hedner T, et al. Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. *Epilepsy Res*. 1995;20:221-227.
172. Marrosu F, Serra A, Maleci A, Puligheddu M, Biggio G, Piga M. Correlation between GABA(A) receptor density and vagus nerve stimulation in individuals with drug-resistant partial epilepsy. *Epilepsy Res*. 2003;55:59-70.
173. Carpenter LL, Moreno FA, Kling MA, et al. Effect of vagus nerve stimulation on cerebrospinal fluid monoamine metabolites, norepinephrine, and gamma-aminobutyric acid concentrations in depressed patients. *Biol Psychiatry.* 2004;56:418-426.
174. Groves DA, Bowman EM, Brown VJ. Recordings from the rat locus coeruleus during acute vagal nerve stimulation in the anaesthetised rat. *Neurosci Lett.* 2005;379:174-179.
175. Lechner SM, Curtis AL, Brons R, Valentino RJ. Locus coeruleus activation by colon distention: role of corticotropin-releasing factor and excitatory amino acids. *Brain Res*. 1997;756:114-124.
176. Hassert DL, Miyashita T, Williams CL. The effects of peripheral vagal nerve stimulation at a memory-modulating intensity on norepinephrine output in the basolateral amygdala. *Behav Neurosci*. 2004;118:79-88.
177. Krahl SE, Clark KB, Smith DC, Browning RA. Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation. *Epilepsia*. 1998;39:709-714.
178. Deuschl G, Wenzelburger R, Kopper F, Volkmann J. Deep brain stimulation of the subthalamic nucleus for Parkinson's disease: a therapy approaching evidence-based standards. *J Neurol*. 2003;250(suppl 1):I43-46.
179. Rodriguez-Oroz MC, Obeso JA, Lang AE, et al. Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. *Brain*. 2005;128(pt 10):2240-2249.
180. Bejjani BP, Damier P, Arnulf I, et al. Transient acute depression induced by high-frequency deep-brain stimulation. *N Engl J Med*. 1999;340:1476-1480.
181. Stefurak T, Mikulis D, Mayberg H, et al. Deep brain stimulation for Parkinson's disease dissociates mood and motor circuits: a functional MRI case study. *Mov Disord*. 2003;18:1508-1516.
182. Mayberg HS, Lozano AM, Voon V, McNeely HE, et al. Deep brain stimulation for treatment-resistant depression. *Neuron*. 2005;45:651-660.
183. McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. *Clin Neurophysiol*. 2004;115:1239-1248.