Neurobiology of Mood Disorders

William R. Marchand, MD
Dott.ssa Valentina Dilda
Cody Roy Jensen, BS

Mood disorders are complex neurobiological conditions.[1,2] For the unipolar disorders—major depression and dysthymic disorder—the mood change is toward one pole of the affective spectrum. For the bipolar conditions—bipolar I disorder, bipolar II disorder, and cyclothymic disorder—the mood changes are toward both ends of the mood spectrum, involving both depressed and manic episodes.

Mood disorders are very common. The lifetime prevalence of major depression in the United States is 10% to 25% in women and 5% to 12% in men.[1] Bipolar disorder is less common, with a prevalence ranging between 2% and 7%.[3–5] These disorders are chronic, cause significant impairment, and frequently can be life threatening.[6–10] Because half of all depressive episodes are treated in a primary care setting rather than by psychiatrists,[11] all physicians need to understand the neuropathology of these conditions.

Traditionally, theories of mood disorder pathology have focused on abnormalities of monoaminergic neurotransmitter systems.[12] Monoaminergic involvement was initially postulated based on the finding that monoamine-depleting agents, such as reserpine, could produce depressive symptoms. This hypothesis was supported by additional evidence showing that monoamine oxidase inhibitors and tricyclic antidepressants increased synaptic levels of norepinephrine and serotonin. Specifically, the monoamine hypothesis stated that depression was the result of insufficient monoaminergic transmission and that these agents produced a therapeutic benefit by normalizing serotonin and norepinephrine levels in the synapse.[13] It is now well accepted that this is an oversimplification and that mood disorder neuropathology must be considered at multiple levels of brain functioning.[12] This article reviews the current understanding of the neurobiology of mood disorders, with a focus on neurologic dysfunction at the levels of the gene, the neuron, neurotransmitters, brain structure, and neurocircuits.

GENETICS OF MOOD DISORDERS

Affective disorders have a strong hereditary component,[14] as demonstrated by family, adoption, twin, and linkage studies.[1] However, the role of genetics in the pathogenesis of mood disorders is complex and is best understood as an inherited vulnerability for developing a mood disorder with nongenetic factors also contributing. Affective disorders exhibit genetic heterogeneity, which means that multiple chromosomal abnormalities may lead to the development of these conditions.[15] For example, associations have been found between mood disorders and genetic markers on chromosomes 5, 11, 13, 18, 22, and X.[1,16]

The mechanism by which genetic abnormalities contribute to the neuropathology of mood disorders remains poorly understood. However, evidence from linkage studies suggests that genetic factors may result in abnormalities of neurotransmitter systems known to be involved in mood disorders, as the following examples illustrate. The dopamine D_2 receptor gene and the gene for tyrosine hydroxylase, which is involved in catecholamine synthesis, are located on candidate chromosomes 5 and 11, respectively. A candidate gene for bipolar disorder, G72, is located on chromosome 13q32. This gene may activate production of the neurotransmitter glutamate. Finally, the GRK3 candidate gene for bipolar disorder is located at chromosome region 22q12. It is thought that as much as 3% to 10% of cases of bipolar disorder can be linked to a single mutation in this gene. GRK3 is one of 6 known genes for G protein receptor kinase 3, which modulates the neuron response to neurotransmitters. While these findings suggest at least some cases of genetic vulnerability may occur by way of alterations in neurotransmitter systems, the exact genetic mechanisms and changes in neurotransmitter function by which this may occur remains unknown. Genetic vulnerability may also be an etiologic

Dr. Marchand is chief of outpatient mental health services, George E. Wahlen VAMC and clinical assistant professor, Department of Psychiatry, University of Utah, Salt Lake City, UT. Dott.ssa Dilda is a graduate student, Department of Psychology, University of Utah, Salt Lake City, UT. Mr. Jensen is a research assistant, George E. Wahlen VAMC, Salt Lake City, UT.

factor for impairment of neuroplasticity, as discussed in the following section.

PATHOLOGY AT THE LEVEL OF THE NEURON

Recently, much research has focused on abnormalities of intracellular signaling pathways in mood disorders.[12,13,17] These complex pathways allow the neuron to process and respond to information and to modulate the signal generated by neurotransmitters.[12] Furthermore, signaling pathways regulate neuroplasticity and cellular resilience by way of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), which activate signaling pathways within the neuron that promote the expression of cytoprotective proteins, such as Bcl-2.[12,17] Neurotrophic factors are necessary for the survival and function of the neuron.[18] Recent evidence has revealed that antidepressants and mood stabilizers enhance the functioning of these pathways,[12] suggesting that mood disorders involve impaired neuroplasticity at the level of the neuron. Additionally, mood disorders are associated with brain changes thought to result from neuron damage and death. Structural imaging and postmortem brain studies have demonstrated reductions in gray matter volumes, glial cell counts, and neuron size in the prefrontal cortex, ventral striatum, hippocampus and amygdala of individuals with mood disorders.[12,19,20]

Impaired neuroplasticity may be caused by several factors, such as an underlying genetic vulnerability, stress-induced cell injury, and damage from multiple mood episodes.[12] Psychosocial stress can lead to impairment of cellular resilience,[12] and it is well known that stress can precipitate episodes of mood symptoms.[21–27] Stress may lead to neuronal damage in individuals genetically predisposed to develop mood disorders. In rodents, it is known that stress can lead to atrophy and death of hippocampal neurons,[28] and in humans depression, it is associated with hippocampal atrophy.[29] Stress-induced neuronal atrophy is believed to be at least partially mediated by activation of the hypothalamic-pituitary-adrenal axis and the resulting high plasma concentrations of glucocorticoids.[28,29] Glucocorticoids may lead to neuronal atrophy by facilitating glutamatergic signaling, which has a role in dendritic remodeling in the hippocampus; by inhibiting glucose transport; and by impairing neurogenesis.[29–31] This mechanism could account for the role of stress in the onset of mood episodes. Finally, multiple mood episodes may lead to further neuronal damage.

Perhaps the most convincing evidence supporting the neuroplasticity hypothesis is the influence of antidepressants and mood stabilizers on neurotrophic pathways that has been demonstrated in trials of these agents.[17] This research has also altered our view of how these agents may work. Antidepressants increase levels of serotonin and norepinephrine at the level of the synapse, and, historically, it was thought that this increase in neurotransmitter levels was the primary mechanism of action of these agents. However, it is now known that increased synaptic concentrations of these neurotransmitters activate intracellular signal transduction cascades,[17] which results in enhanced expression of BDNF and its receptor.[17,30,32] Furthermore, there is evidence that these neurotrophic effects result in regeneration of catecholamine axon terminals in the cortex, enhance synaptic plasticity in the hippocampus, and may attenuate hippocampal atrophy.[30,32] Finally, infusion of BDNF into the midbrain has an antidepressant-like influence on animal models of depression, providing additional evidence that antidepressant-induced upregulation of BDNF may contribute to the therapeutic mechanism of these agents.[33,34]

In regard to mood stabilizers, it has been established that lithium increases the levels of Bcl-2 in the rodent brain and cells of human neuronal origin.[35,36] In human clinical studies, lithium treatment has been shown to increase a marker of neuron function in gray matter[37] and increase total gray matter content in the brain.[38] The mood stabilizer valproate also activates Bcl-2, and both agents increase the expression of BDNF.[17]

Finally, there is evidence that 2 nonpharmacologic treatments for depression may have neurotrophic effects. Both transcranial magnetic stimulation and electroconvulsive therapy have been shown to influence BDNF.[17] Taken together, these studies provide compelling evidence that mood disorders are, at least in part, disorders of neuroplasticity and that many treatments for these disorders act by enhancing nerve cell health and survival. **Table 1** summarizes the evidence supporting the neuroplasticity hypothesis of mood disorders.

NEUROTRANSMITTER ABNORMALITIES

Historically, serotonin, norepinephrine, and dopamine were the primary neurotransmitters implicated in mood disorders. It is now known that other neurotransmitters, including acetylcholine, histamine, γ-aminobutyric acid (GABA), and glutamate, also contribute to the pathophysiology of these disorders.[39]

Serotonin

The serotonin system originates in the raphe nuclei of the midbrain and projects to the limbic system as well as the basal ganglia, thalamus, cortex, and cerebellum.

Mood disorders are associated with a functional decrease in serotonin neurotransmission,[40] which may be due to the excessive reuptake of the serotonin released by the presynaptic cell. The dorsal raphe nucleus is responsible for regulating the sleep-wake switch in the brain. When the level of serotonin produced by this nucleus is altered, patients with mood disorder can experience insomnia.[41] Patients with bipolar disorder exhibit impaired sleep efficiency, higher levels of anxiety and fear about poor sleep, and a tendency to misperceive sleep.[42] Alterations in the serotonin system are also related to suicidal behavior. Evidence from autopsies of suicide victims has revealed low levels of serotonin,[43] and serotonergic raphe neurons showed altered activity in patients with mood disorders who completed suicide as compared to those without suicidal behavior.[44]

Norepinephrine

The norepinephrine system originates in both the ventrolateral tegmental area (a nucleus in the midbrain and the locus caeruleus (a small nucleus in the brainstem). The ventrolateral tegmental area projects to the hypothalamus and the reticular formation (a diffusely organized group of cells in the brainstem), while the locus caeruleus projects to the thalamus, hypothalamus, cortex, and prefrontal cortex. These projections influence feeding, sexual behavior, and sleep as well as cognitive functions. Studies suggest that lower norepinephrine concentrations are present in unipolar depression and higher concentrations in bipolar patients. Low levels of norepinephrine have been associated with cognitive dysfunction, dysphoria, fatigue, and apathy.

Dopamine

Three dopaminergic subsystems regulate motor activity and cognitive functioning. In the nigrostriatal system, dopamine originates from the substantia nigra (a nucleus of the midbrain) and projects to the dorsal portion of the striatum (nucleus accumbens, caudate and putamen). This system regulates selection and execution of motor behaviors. The mesolimbic system originates in the ventral tegmental area and projects to the ventral striatum and prefrontal cortex. This system is involved with regulation of emotion and response to reward. The mesocortical system also originates in the ventral tegmental area but projects to the motor and premotor cortex as well as the dorsolateral prefrontal cortex. This system is involved with movement and problem solving.

Dopamine release into the ventral striatum results in the experience of pleasure, which provides reinforcement to motivate persons to take actions necessary for survival, such as eating or procreating. During depressive episodes, the concentration of dopamine is consistently reduced, especially in the mesolimbic system. Therefore, depressed patients experience loss of motivation and interest, physical slowing, and a lack of pleasure. Dopamine abnormalities have also been associated with hyperactive behavior in mania.

Table 1. Evidence for Impaired Neuroplasticity in Mood Disorders

Psychosocial stress often precipitates mood episodes and is linked to impaired neuroplasticity
Atrophy in mood disorders is likely secondary to impaired neuroplasticity
Antidepressants increase the neurotrophic factor BDNF
Mood stabilizers increase the neurotrophic factors BDNF and Bcl-2
Transcranial magnetic stimulation and electroconvulsive therapy increase the neurotrophic factor BDNF

BDNF = brain-derived neurotrophic factor.

Data from references 12, 13, 17–20.

GABA and Glutamate

GABA and glutamate are respectively the main inhibitory and excitatory amino-acid neurotransmitters, and both have been implicated in mood disorders. Some studies suggest that unipolar patients have lower concentrations of GABA.[45,46] Decreased synthesis and release of GABA is also present in response to acute and chronic stress. Recent studies have found that higher concentrations of glutamate can be associated with depression,[47] and increased levels of glutamate in bipolar patients have been reported.[48,49]

Acetylcholine

Acetylcholine is the neurotransmitter utilized by the cholinergic system. This system projects from the basal forebrain nucleus to almost all portions of the cortex. As a consequence, this neurotransmitter produces multiple effects on neuronal and mental functioning. In particular, acetylcholine is critical in motor behavior, memory functioning, and cognitive performance. There is some evidence linking abnormalities of this neurotransmitter with mood disorders, although further research is needed.[50]

Histamine

Histaminergic neurons originate in the posterior hypothalamus and project to the limbic system and neocortex. These neurons regulate learning and memory, endocrine homeostasis, and primary needs such as food, water, and sleep.[51] High levels of histamine have

Table 2. Symptoms Associated with Neurotransmitter Abnormalities in Mood Disorders

Neurotransmitter	Symptom
Serotonin	Sleep disturbance
	Suicide
Norepinephrine	Cognitive dysfunction
	Dysphoria
	Fatigue
	Apathy
Dopamine	Psychomotor changes
	Loss of motivation
GABA and glutamate	Implicated in mood disorders but not associated with specific symptoms
Histamine	Severity of depressive symptoms

Data from references 41–44, 53.

GABA = γ-aminobutyric acid.

been associated with depressive symptoms, and recent research suggests that decreased histamine H_1 receptor may correlate with the severity of depressive symptoms.[52] **Table 2** summarizes symptoms associated with neurotransmitter abnormalities in mood disorders.

ABNORMALITIES IN BRAIN STRUCTURE AND FUNCTION

An association between changes in both brain structure and function and mood disorders has been supported by many postmortem and structural and functional imaging studies (**Table 3**).[19,54–71]

Frontal Cortex

The frontal cortex (**Figure 1**) is responsible for controlling movements as well as higher level thinking, attention, and executive functions. In both unipolar and bipolar disorder, there is a general decrease in prefrontal cortex volume[53] as well as blood flow and metabolism.[54] However, some studies have reported that decreased activity of the left frontal cortex is associated with depressive symptoms and that dysfunction involving the right frontal cortex is associated with mania.[72] The prefrontal region seems to be more strongly linked to mood disorders than other frontal areas. The prefrontal cortex is involved with executive functioning, mood regulation, expression of personality, and social behavior. Two prefrontal regions, the orbitofrontal cortex (OFC; involved with decision-making) and the dorsolateral prefrontal cortex (DLPFC; involved with attention, memory, motivational states, and goal-directed behavior) have been implicated in mood disorders. Numerous studies have reported hyperactivity of the OFC[55,73] and a reduction of activity in DLPFC in patients with depression.[19,56] The DLPFC exhibits reduced blood flow and metabolism in patients with major depression, whereas in healthy individuals the metabolic rate in this area increases in response to emotional stimuli.[57]

Table 3. Structural and Functional Abnormalities Associated with Mood Disorders

Frontal cortex
General volume reduction in bipolar and unipolar illness
General decreased activity in bipolar and unipolar illness
Decreased activity of dorsolateral prefrontal cortex in unipolar depression
Increased activity of orbitofrontal cortex in unipolar depression
Amygdala
Increased volume in bipolar disorder
Decreased volume in unipolar depression
Hippocampus
Decreased volume in the elderly with unipolar depression
Cingulate cortex
Variable changes in activity
Striatum
Increased volume in bipolar disorder
Decreased volume in unipolar depression
Cerebellum
Decreased vermis volume in unipolar depression

Data from references 54–71.

Amygdala

The amygdala (Figure 1) plays a central role in the emotional aspects of learning and emotional responses to stimuli. Studies have shown that lesions of the amygdala interfere with processing of emotional information. In particular, the amygdala is involved in perception of and reaction to fear. Neuroimaging studies have shown increased activity in this area in response to fearful stimuli. Amygdala enlargement in bipolar patients has been reported in a number of studies.[58,74–76] Although amygdala enlargement is a normal consequence of aging, adolescents with bipolar disorder experience early-onset enlargement, which suggests that enlargement is a developmental abnormality.[77] Some patients with unipolar depression have a volume reduction in the right amygdala,[78] and a significant bilateral volume reduction has been found in depressed children.[79]

Hippocampus

The hippocampus is also thought to be involved in both unipolar and bipolar depression. The hippocampus is primarily involved with memory and the analysis of information about the context in which events occur. The ability to process contextual information is necessary for the regulation of emotional expression. Studies of the hippocampus and depression have reported conflicting findings, with one showing no association between hippocampal abnormalities and mood disorders,[80] and another showing significant hippocampal volume reduction in elderly patients with unipolar disease.[81]

Cingulate Cortex

The cingulate cortex regulates aspects of cognitive functioning, emotions, decision-making, attention, and social behavior. Increased cingulate activity is found in healthy subjects during positive emotional states[59] and in patients with mood disorder during depression.[82] Increased activity in the left dorsal anterior cingulate[83,84] has been found in some patients with bipolar disorder, but decreased cingulate activity has been found in others.[85,86]

Ventricles and Blood Flow

Enlarged ventricles are common in patients with both unipolar and bipolar illness.[87,88] Enlargement of the third and the fourth ventricles has been reported in adult and adolescent bipolar patients as early as after the first episode of mania.[89,90] Ventricular expansion seems to be correlated with the number of prior affective episodes[91] and may be due to decreased tissue volumes in the periventricular brain regions.[77] Some studies have also reported periventricular white matter hyperintensities for elderly bipolar patients, although the significance of these findings is unclear.[92]

Both increased and decreased blood flow in specific brain regions have been found in patients with mood disorder. A number of studies have reported abnormalities in cerebral blood flow in patients affected by major depression.[93,94] In particular, studies of regional cerebral blood flow have found a more pronounced blood flow abnormality in the left hemisphere of patients with major depression.[95] Decreased cerebral blood flow in the left hemisphere has also been reported in bipolar patients when compared with unipolar and healthy patients.[96]

Subcortical Structures

Increased striatal volume in bipolar patients has been reported in a number of studies,[60,97] and a reduction in volume in the ventral striatal region has been associated with major depression. Decreased volumes of the caudate, putamen, and globus pallidus (Figure 1) have been found in patients with unipolar depression[61–63] in some studies but not in others.[64–66] Some studies have reported increased volumes of the caudate and globus pallidus in bipolar disorder patients,[76] but others suggest no significant difference.[67,90] Thalamic enlargement has also been reported in bipolar disorder[68,76] but not in association with unipolar symptoms.[69]

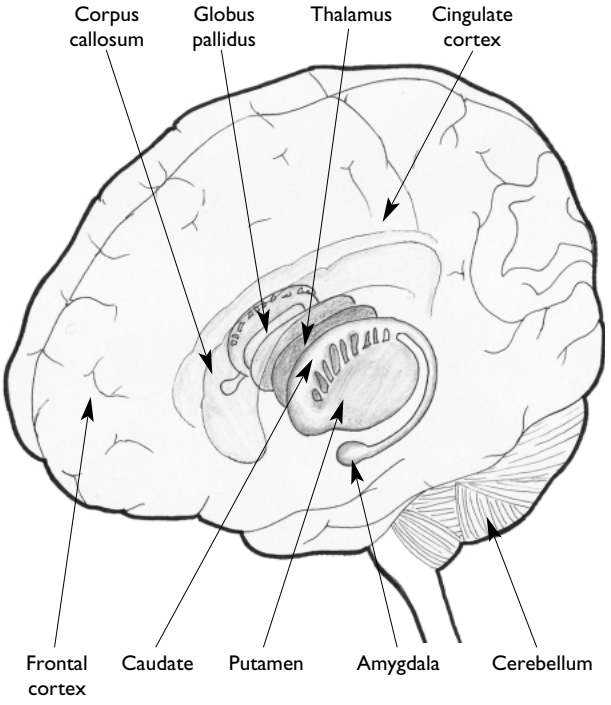

Figure 1. Selected brain structures involved in the neuropathology of mood disorders. The amygdala is the primary structure involved with the processing of emotion and response to the environment. The basal ganglia and thalamus are important structures in the frontal-subcortical circuits.

Cerebellum

The cerebellum (Figure 1) is involved in modulation of movements and regulation of muscle tone. However, regions of the cerebellum receive projections from the prefrontal and temporal regions[70] and limbic structures.[98,99] Direct projections from the cerebellum to the hypothalamus have also been found.[100] Further, lesions occurring in the cerebro-ponto-cerebellar pathways may play a role in pathologic laughter or crying.[101] These data suggest that the cerebellum is involved with modulation of emotions. Recent findings suggest that although the overall size of the cerebellum does not vary in patients with mood disorders, vermis

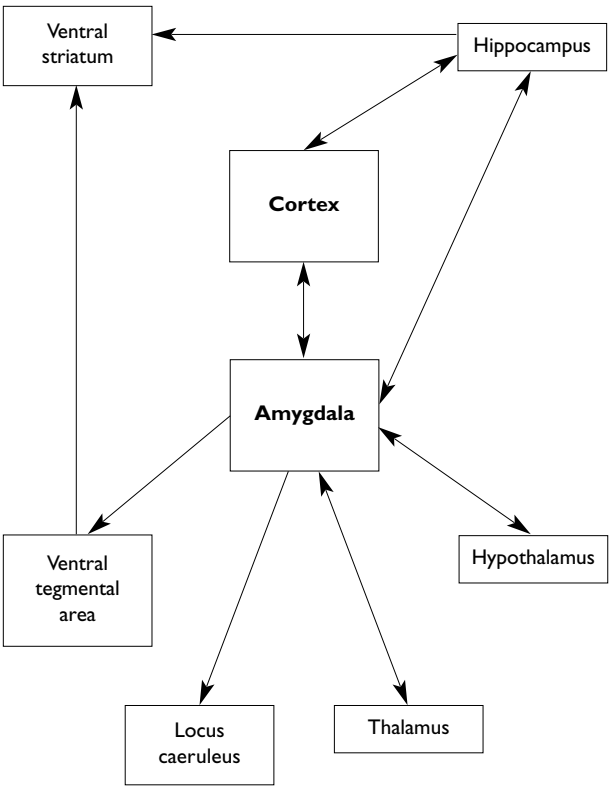

Figure 2. General organizational structure of the limbic circuits and major connections. The amygdala is the structure most involved with formulating emotional response, particularly fear, and determining one's affective perceptions of sensory stimuli. The amygdala receives sensory and body status information from multiple brain areas. The outflow of information from the amygdala provides control over the body's response to the environment. As a response to stressful situations, amygdala output to the hypothalamus results in sympathetic nervous system activation (fight or flight response) and in the "stress hormone response" of corticosteroid release. The cognitive experience of emotion is mediated by connections from the amygdala to the cortex. Finally, amygdala input to the locus caeruleus and ventral tegmental area control the release of norepinephrine and dopamine release, respectively.

atrophy may be present in patients with major depression.[102] The vermis seems to be strongly interconnected with limbic brain regions,[71] which might account for its role in affective disorders. Finally, bipolar patients seem to exhibit a smaller ventral cerebellum as compared with healthy individuals.[103]

PATHOLOGY OF NEUROCIRCUITS

Brain structures are connected by nerve fibers to form circuits that allow structures to communicate and process information. Further, circuits provide the means for structures to coordinate output, such as controlling motor function. One well-known circuit is the limbic system (**Figure 2**), which influences many aspects of emotional behavior. The limbic system determines response to stimuli that evoke fear or pleasure.[104] Given the role of this circuit in emotional processing, it is easy to understand why it is involved in the pathology of mood disorders. Limbic structures include the cingulate cortex, basal temporal cortex, hippocampus, anterior thalamus, and the amygdala.

The amygdala is the primary limbic structure. It receives inputs from multiple areas, and the outflow of information from the amygdala provides control over the body's response to the environment. External sensory inputs provide information about the environment, including olfactory input from the olfactory bulb, visual information from the inferior temporal cortex, and auditory information from the thalamus. Internal information about the current state of bodily functions comes from the hypothalamus. The appropriate response to the environment and state of the body is determined by cognitive processing of information from the cingulate gyrus and prefrontal association cortices and memory information from the hippocampus.[104] For example, in response to potentially dangerous situations, amygdala output results in sympathetic nervous system activation (fight or flight response) by way of the hypothalamus. Also, output to the reticular pontine nuclei leads to the startle response, and output to the central gray nucleus leads to the freezing behavior seen in fear states. Connections from the amygdala to the hypothalamus result in adrenocorticotropin release and the "stress hormone response" of corticosteroid release. The cognitive experience of emotion is mediated by connections from the amygdala to the cingulate gyrus and orbitofrontal cortex. Finally, amygdala input to the locus caeruleus and ventral tegmental area control the release of norepinephrine and dopamine release, respectively.

The frontal-subcortical (FSC) circuits (**Figure 3**) are also implicated in mood disorder pathology. These circuits are involved with motor, cognitive, and emotional processing, and evidence is accumulating that they play a role in a number of neuropsychiatric disorders.[105,106] FSC circuits share a general structure in which information originating from many areas in the cerebral cortex travels first to the basal ganglia then on to the thalamus, and finally returns to the cortex. There are complex connections between the FSC and limbic circuits, and dopamine fibers provide the major connections.

Several lines of evidence implicate abnormalities in the limbic and FSC circuits in affective disorders. Lesion studies have revealed that damage to structures

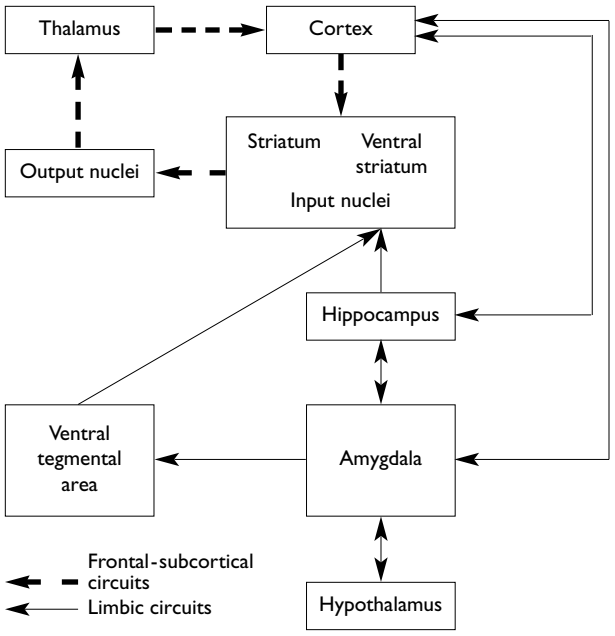

Figure 3. Depiction of the complex relationship between the limbic and frontal-subcortical circuits (FSC; not all connections are shown). Dopamine fibers provide one of the major mechanisms by which the limbic system influences FSC circuits. Afferents from the amygdala to the ventral tegmental area control dopamine release. Fibers from the ventral tegmental area project to the ventral striatum by way of the mesolimbic dopamine pathway. Projections from the ventral striatum to the substantia nigra influence dopamine release by way of the nigrostriatal dopamine pathway. Thus, the ventral striatum, by way of projections to the substantia nigra, is able to exert global regulatory influence on dopaminergic input to the entire striatum.

of the FSC circuits produce symptoms similar to those seen in mood disorders. Direct evidence for limbic and FSC circuit pathology in mood disorders includes the structural and functional abnormalities of structures and neurotransmitters described above. **Table 4** outlines evidence that supports limbic and FSC dysfunction as a component of mood disorders.

Table 4. Evidence for Limbic and Frontal-Subcortical Circuit Abnormalities in Mood Disorders

Evidence supporting limbic circuit pathology
Amygdala volumetric abnormalities
Hippocampus volumetric abnormalities
Norepinephrine abnormalities
Evidence supporting frontal-subcortical circuit pathology
Thalamus volume abnormalities
Basal ganglia volume abnormalities
GABA abnormalities
Glutamate abnormalities
Evidence supporting both limbic and frontal-subcortical circuit pathology
Dopamine abnormalities
Frontal cortex volumetric and functional abnormalities
Cingulate cortex functional abnormalities

Data from references 19, 41–44, 54–71.

GABA = γ-aminobutyric acid.

CONCLUSION

Significant progress has been made in our understanding of the neurobiology of mood disorders. It is possible to say with certainty that mood disorders are inherited conditions, with bipolar spectrum illness having a stronger genetic component than unipolar spectrum illness. However, the actual inherited vulnerability remains unknown. There is compelling evidence that mood disorders are associated with impairments of neuroplasticity. It is possible that impaired neuroplasticity is the primary pathology of these disorders. However, it is also possible that loss of neuroplasticity actually represents damage to neurotrophic systems from multiple mood episodes. Abnormalities in the neurotransmitter systems have been identified in affective disorders, but again, it is unclear if these abnormalities are part of the primary pathology or are secondary to structural and functional abnormalities at the level of the neuron and/or neurocircuit. Finally, there is considerable evidence linking structural and functional pathology of the limbic and FSC and structures with mood disorder, and this pathology may be secondary to impaired neuronal functioning.

Our changing understanding of the neurobiology of mood disorders has a number of potential clinical implications. Perhaps most important is the recognition that mood disorders in many, if not all, cases appear to involve chronic neurodegeneration caused by impaired neuroplasticity and/or neuronal damage from repeated mood episodes. Clinicians, therefore, must manage mood disorders as they would other progressive illnesses, with a focus not only on achieving remission of particular episodes but also on prevention of further neuronal damage. If further research substantiates early findings that some psychotropic agents enhance neuroplasticity, it is possible that these medications will be used for this purpose alone, even if medical therapy is not required to control symptoms. For example, lithium might be used routinely for individuals with unipolar depression whose symptoms respond adequately to conventional antidepressants. While there is currently insufficient evidence to support this

approach, the concept of neurodegeneration strongly supports the practice of long-term maintenance treatment for those with a chronic form of mood disorder. Current evidence suggests that long-term treatment may not only prevent relapse but actually may help repair neuronal damage. Although additional research will be needed to determine the outcomes of long-term treatment, the possibility of reversing the effects of neurodegeneration supports the current standard of care (ie, long-term treatment for individuals with bipolar illness and for those with recurrent unipolar illness.)

Much work remains to be done to further our understanding of the neuropathology of mood disorders. However, the progress made to date clearly establishes that these are neurobiological conditions. Hopefully, this information will decrease the stigma associated with mood disorders and inspire further research efforts. **HP**

This work was supported in part by the Veterans Administration VISN 19 MIRECC.

Test your knowledge and comprehension of this article with *Review Questions* on page 36.

REFERENCES

1. Sadock BJ, Sadock VA. Mood disorders. In: Sadock BJ, Sadock VA, editors. Kaplan & Sadock's synopsis of psychiatry: behaviorial sciences, 9th editor Philadelphia: Lippincott Williams & Wilkins; 2003:534–90.
2. Diagnostic and statistical manual of mental disorders: DSM-IV-TR. 4th ed., text revision. Washington (DC): American Psychiatric Association; 2000.
3. Angst J. The emerging epidemiology of hypomania and bipolar II disorder. J Affect Disord 1998;50:143–51.
4. Goodwin FK, Ghaemi SN. The difficult-to-treat patient with bipolar disorder. In: Dewan MJ, Pies RW, editors. The difficult-to-treat psychiatric patient. Washington (DC): American Psychiatric; 2001:7–39.
5. Akiskal HS. The prevalent clinical spectrum of bipolar disorders: beyond DSM-IV. J Clin Psychopharmacol 1996;16(2 Suppl 1):4S–14S.
6. Hirschfeld RM. Bipolar spectrum disorder: improving its recognition and diagnosis. J Clin Psychiatry 2001;62 Suppl 14:5–9.
7. Goodwin FK, Jamison KR. Manic-depressive illness. New York: Oxford University Press; 1990:227–44.
8. Isometsa ET, Henriksson MM, Aro HM, Lonnqvist JK. Suicide in bipolar disorder in Finland. Am J Psychiatry 1994;151:1020–4.
9. Practice guideline for the treatment of patients with major depressive disorder. 2nd ed. Washington (DC): American Psychiatric Association; 2000:463–545.
10. Practice guideline for the treatment of patients with bipolar disorder. 2nd ed. Washington (DC): American Psychiatric Association; 2002:547–634.
11. Docherty JP. Barriers to the diagnosis of depression in primary care. J Clin Psychiatry 1997;58 Suppl 1:5–10.
12. Manji HK, Drevets WC, Charney DS. The cellular neurobiology of depression. Nat Med 2001;7:541–7.
13. Laifenfeld D, Klein E, Ben-Shachar D. Norepinephrine alters the expression of genes involved in neuronal sprouting and differentiation: relevance for major depression and antidepressant mechanisms. J Neurochem 2002;83: 1054–64.
14. McGuffin P, Rijsdijk F, Andrew M, et al. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch Gen Psychiatry 2003;60: 497–502.
15. Merikangas KR, Risch N. Will the genomics revolution revolutionize psychiatry? Am J Psychiatry 2003;160:625–35.
16. Potash JB, Zandi PP, Willour VL, et al. Suggestive linkage to chromosomal regions 13q31 and 22q12 in families with psychotic bipolar disorder. Am J Psychiatry 2003;160:680–6.
17. Hashimoto K, Shimizu E, Iyo M. Critical role of brain-derived neurotrophic factor in mood disorders. Brain Res Brain Res Rev 2004;45:104–14.
18. Back IB. Trophic regulation of synaptic plasticity. J Neurobiol 1999;41:108–18.
19. Drevets WC. Neuroimaging studies of mood disorders. Biol Psychiatry 2000;48:813–29.
20. Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. Biol Psychiatry 2000;48:766–77.
21. Kessler RC. The effects of stressful life events on depression. Annu Rev Psychol 1997;48:191–214.
22. Lam DH, Watkins ER, Hayward P, et al. A randomized controlled study of cognitive behavior therapy for relapse prevention for bipolar affective disorder: outcome of the first year. Arch Gen Psychiatry 2003;60:145–52.
23. Frank E, Swartz HA, Kupfer DJ. Interpersonal and social rhythm therapy: managing the chaos of bipolar disorder. Biol Psychiatry 2000;48:593–604.
24. Ellicott A, Hammen C, Gitlin M, et al. Life events and the course of bipolar disorder. Am J Psychiatry 1990;147: 1194–8.
25. Miklowitz DJ, Goldstein MJ, Nuechterlein KH, et al. Family factors and the course of bipolar affective disorder. Arch Gen Psychiatry 1988;45:225–31.
26. Miklowitz DJ, Simoneau TL, George EL, et al. Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. Biol Psychiatry 2000:48:582–92.
27. O'Connell RA, Mayo JA, Flatow L, et al. Outcome of biploar disorder on long-term treatment with lithium. Br J Psychiatry 1991:159:123–9.
28. McEwen BS. Stress and hippocampal plasticity. Annu Rev Neurosci 1999;22:105–22.
29. Sapolsky RM. Glucocorticoids and hippocampal atrophy

in neuropsychiatric disorders. Arch Gen Psychiatry 2000;57:925–35.
30. Duman RS, Malberg J, Nakagawa S, D'Sa C. Neuronal plasticity and survival in mood disorders. Biol Psychiatry 2000;48:732–9.
31. Jacobs BL, Praag H, Gage FH. Adult brain neurogenesis and psychiatry: a novel theory of depression. Mol Psychiatry 2000;5:262–9.
32. Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. Arch Gen Psychiatry 1997; 54:597–606.
33. Siuciak JA, Lewis DR, Wiegand SJ, Lindsay RM. Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). Pharmacol Biochem Behav 1997;56: 131–7.
34. Shiryama Y, Chen AC, Nakagawa S, et al. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. J Neurosci 2002;22: 3251–61.
35. Chen G, Zeng WZ, Yuan PX, et al. The mood-stabilizing agents lithium and valproate robustly increase the levels of the neuroprotective protein Bcl-2 in the CNS. J Neurochem 1999;72:879–82.
36. Chen RW, Chuang DM. Long term lithium treatment suppresses p53 and Bax expression but increases Bcl-2 expression. A prominent role in neuroprotection against excitotoxicity. J Biol Chem 1999;274:6039–42.
37. Moore GJ, Bebchuk JM, Hasanat K, et al. Lithium increases N-acetyl-aspartate in the human brain: in vivo evidence in support of Bcl-2's neurotrophic effects? Biol Psychiatry 2000;48:1–8.
38. Moore GJ, Bebchuk JM, Wilds IB, et al. Lithium-induced increase in human brain grey matter [published erratum appears in Lancet 2000;356:2104] [letter]. Lancet 2000; 356:1241–2.
39. Sanacora G, Rothman DL, Mason G, Krystal JH. Clinical studies implementing glutamate neurotransmission in mood disorders. Ann N Y Acad Sci 2003;1003:292–308.
40. Delgado PL, Miller HL, Salomon RM, et al. Tryptophan-depletion challenge in depressed patients treated with desipramine or fluoxetine: implications for the role of serotonin in the mechanism of antidepressant action. Biol Psychiatry 1999;46:212–20.
41. Adrien J. Neurobiological bases for the relation between sleep and depression. Sleep Med Rev 2002;6:341–51.
42. Harvey AG, Schmidt DA, Scarna A, et al. Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. Am J Psychiatry 2005;162:50–7.
43. Courtet P, Jollant F, Castelnau D, et al. Suicidal behavior: relationship between phenotype and serotonergic genotype. Am J Med Genet C Semin Med Genet 2005;133: 25–33.
44. Arango V, Underwood MD, Boldrini M, et al. Serotonin 1A receptors, serotonin transporter binding and serotonin transporter mRNA expression in the brainstem of depressed suicide victims. Neuropsychopharmacology 2001;25:892–903.
45. Bjork JM, Moeller FG, Kramer GL, et al. Plasma GABA levels correlate with aggressiveness in relatives of patients with unipolar depressive disorder. Psychiatry Res 2001;101:131–6.
46. Petty F, Kramer GL, Gullion CM, Rush AJ. Low plasma gamma-aminobutyric acid levels in male patients with depression. Biol Psychiatry 1992;32:354–63.
47. Mauri MC, Ferrara A, Boscati L, et al. Plasma and platelet amino acid concentrations in patients affected by major depression and under fluvoxamine treatment. Neuropsychobiology 1998;37:124–9.
48. Michael N, Erfurth A, Ohrmann P, et al. Acute mania is accompanied by elevated glutamate/glutamine levels within the left dorsolateral prefrontal cortex. Psychopharmacology (Berl) 2003;168:344–6.
49. Kalkman HO, Loetscher E. GAD(67): the link between the GABA-deficit hypothesis and the dopaminergic and glutamatergic theories of psychosis. J Neural Transm 2003;110:803–12.
50. Janowsky DS, Overstreet DH, Nurnberger JI Jr. Is cholinergic sensitivity a genetic marker for the affective disorders? Am J Med Genet 1994;54:335–44.
51. Brown RE, Stevens DR, Haas HL. The physiology of brain histamine. Prog Neurobiol 2001;63:63772.
52. Kano M, Fukudo S, Tashiro A, et al. Decreased histamine H_1 receptor binding in the brain of depressed patients. Eur J Neurosci 2004;20:803–10.
53. Strakowski SM, Adler CA, DelBello MP. Volumetric MRI studies of mood disorders: do they distinguish unipolar and bipolar disorder? Bipolar Disord 2002;4:80–8.
54. Soares JC, Mann JJ. The functional neuroanatomy of mood disorders. J Psychiatr Res 1997;31:393–432.54.
Biver F, Goldman S, Delvenne V, et al. Frontal and parietal metabolic disturbances in unipolar depression. Biol Psychiatry 1994;36:381–8.
55. Biver F, Goldman S, Delvenne V, et al. Frontal and parietal metabolic disturbances in unipolar depression. Biol Psychiatry 1994;36:381–8.
56. Baxter LR Jr, Schwartz JM, Phelps ME, et al. Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatry 1989;46:243–50.
57. Reiman EM, Lane RD, Ahern GL, et al. Neuroanatomical correlates of externally and internally generated human emotion. Am J Psychiatry 1997;154:918–25.
58. Brambilla P, Harenski K, Nicoletti M, et al. MRI investigation of temporal lobe structures in bipolar patients. J Psychiatr Res 2003;37:287–95.
59. Teasdale JD, Howard RJ, Cox SG, et al. Functional MRI study of the cognitive generation of affect. Am J Psychiatry 1999;156:209–15.
60. Noga JT, Vladar K, Torrey EF. A volumetric magnetic resonance imaging study of monozygotic twins discordant for bipolar disorder. Psychiatry Res 2001;106:25–34.
61. Lacerda AL, Nicoletti MA, Brambilla P, et al. Anatomical MRI study of basal ganglia in major depressive disorder. Psychiatry Res 2003;124:129–40.

62. Clark LM, McDonald WM, Welsh-Bohmer KA, et al. Magnetic resonance imaging correlates of depression in early- and late-onset Alzheimer's disease. Biol Psychiatry 1998;44:592–9.
63. Krishnan KR, McDonald WM, Doraiswamy PM, et al. Neuroanatomical substrates of depression in the elderly. Eur Arch Psychiatry Clin Neurosci 1993;243:41–6.
64. Dupont RM, Jernigan TL, Heindel W, et al. Magnetic resonance imaging and mood disorders. Localization of white matter and other subcortical abnormalities. Arch Gen Psychiatry 1995;52:747–55.
65. Lenze EJ, Sheline YI. Absence of striatal volume differences between depressed subjects with no comorbid medical illness and matched comparison subjects. Am J Psychiatry 1999;156:1989–91.
66. Aylward EH, Harris GJ, Hoehn-Saric R, et al. Normal caudate nucleus in obsessive-compulsive disorder assessed by quantitative neuroimaging. Arch Gen Psychiatry 1996;53:577–84.
67. Sax KW, Strakowski SM, Zimmerman ME, et al. Frontosubcortical neuroanatomy and the continuous performance test in mania. Am J Psychiatry 1999;156:139–41.
68. Dupont RM, Butters N, Schafer K, et al. Diagnostic specificity of focal white matter abnormalities in bipolar and unipolar mood disorder. Biol Psychiatry 1995;38:482–6.
69. Starkstein SE, Fedoroff P, Berthier ML, Robinson RG. Manic-depressive and pure manic states after brain lesions. Biol Psychiatry 1991;29:149–58.
70. Schmahmann JD, Pandya DN. The cerebrocerebellar system. Int Rev Neurobiol 1997;41:31–60.
71. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain 1998;121(Pt 4):561–79.
72. Joseph R. Frontal lobe psychopathology: mania, depression, confabulation, catatonia, perseveration, obsessive compulsions, and schizophrenia. Psychiatry 1999;62: 138–72.
73. Baker SC, Frith CD, Dolan RJ. The interaction between mood and cognitive function studied with PET. Psychol Med 1997;27:565–78.
74. Altshuler LL, Bartzokis G, Grieder T, et al. Amygdala enlargement in bipolar disorder and hippocampal reduction in schizophrenia: an MRI study demonstrating neuroanatomic specificity [letter]. Arch Gen Psychiatry 1998;55:663–4.
75. Altshuler LL, Bartzokis G, Grieder T, et al. An MRI study of temporal lobe structures in men with bipolar disorder or schizophrenia. Biol Psychiatry 2000;48:147–62.
76. Strakowski SM, DelBello MP, Sax KW, et al. Brain magnetic resonance imaging of structural abnormalities in bipolar disorder. Arch Gen Psychiatry 1999;56:254–60.
77. Strakowski SM, Delbello MP, Adler CM. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. Mol Psychiatry 2005;10:105–16.
78. Xia J, Chen J, Zhou Y, et al. Volumetric MRI analysis of the amygdala and hippocampus in subjects with major depression. J Huazhong Univ Sci Technolog Med Sci 2004;24:500–2, 506.
79. Rosso IM, Cintron CM, Steingard RJ, et al. Amygdala and hippocampus volumes in pediatric major depression. Biol Psychiatry 2005;57:21–6.
80. Mervaala E, Fohr J, Kononen M, et al. Quantitative MRI of the hippocampus and amygdala in severe depression. Psychol Med 2000;30:117–25.
81. Ashtari M, Greenwald BS, Kramer-Ginsberg E, et al. Hippocampal/amygdala volumes in geriatric depression. Psychol Med 1999;29:629–38.
82. Mayberg HS, Brannan SK, Mahurin RK, et al. Cingulate function in depression: a potential predictor of treatment response. Neuroreport 1997;8:1057–61.
83. Blumberg HP, Stern E, Martinez D, et al. Increased anterior cingulate and caudate activity in bipolar mania. Biol Psychiatry 2000;48:1045–52.
84. Rubinsztein JS, Fletcher PC, Rogers RD, et al. Decision-making in mania: a PET study. Brain 2001;124(Pt 12): 2550–63.
85. Sassi RB, Brambilla P, Hatch JP, et al. Reduced left anterior cingulate volumes in untreated bipolar patients. Biol Psychiatry 2004;56:467–75.
86. Brambilla P, Nicoletti MA, Harenski K, et al. Anatomical MRI study of subgenual prefrontal cortex in bipolar and unipolar subjects. Neuropsychopharmacology 2002;27: 792–9.
87. Rabins PV, Pearlson GD, Aylward E, et al. Cortical magnetic resonance imaging changes in elderly inpatients with major depression. Am J Psychiatry 1991;148:617–20.
88. Iidaka T, Nakajima T, Kawamoto K, et al. Signal hyperintensities on brain magnetic resonance imaging in elderly depressed patients. Eur Neurol 1996;36:293–9.
89. Friedman L, Findling RL, Kenny JT, et al. An MRI study of adolescent patients with either schizophrenia or bipolar disorder as compared to healthy control subjects [published erratum appears in Biol Psychiatry 1999;46: following 584]. Biol Psychiatry 1999;46:78–88.
90. Strakowski SM, Wilson DR, Tohen M, et al. Structural brain abnormalities in first-episode mania. Biol Psychiatry 1993;33:602–9.
91. Brambilla P, Harenski K, Nicoletti M, et al. MRI study of posterior fossa structures and brain ventricles in bipolar patients. J Psychiatr Res 2001;35:313–22.
92. Silverstone T, McPherson H, Li Q, Doyle T. Deep white matter hyperintensities in patients with bipolar depression, unipolar depression and age-matched control subjects. Bipolar Disord 2003;5:53–7.
93. Sackeim HA, Prohovnik I. Brain imaging studies in depressive disorders. In: Mann JJ, Kupfer DJ, editors. Biology of depressive disorders. New York: Plenum; 1993:205–58.
94. Drevets WC. Functional neuroimaging studies of depression: the anatomy of melancholia. Annu Rev Med 1998; 49:341–61.
95. Mjaland O, Normann E, Halvorsen E, et al. [Regional cerebral perfusion before and after parathyroidectomy.] [Article in Norwegian.] Tidsskr Nor Laegeforen 2005; 125:33–5.

(continued on page 43)

(from page 26)

96. Delvenne V, Delecluse F, Hubain PP, et al. Regional cerebral blood flow in patients with affective disorders. Br J Psychiatry 1990;157:359–65.
97. Aylward EH, Roberts-Twillie JV, Barta PE, et al. Basal ganglia volumes and white matter hyperintensities in patients with bipolar disorder. Am J Psychiatry 1994;151: 687–93.
98. Anand BK, Malhotra CL, Singh B, Dua S. Cerebellar projections to limbic system. J Neurophysiol 1959;22:451–7.
99. Heath RG, Dempesy CW, Fontana CJ, Myers WA. Cerebellar stimulation: effects on septal region, hippocampus, and amygdala of cats and rats. Biol Psychiatry 1978;13:501–29.
100. Dietrichs E. Cerebellar autonomic function: direct hypothalamocerebellar pathway. Science 1984;223:591–3.
101. Parvizi J, Anderson SW, Martin CO, et al. Pathological laughter and crying: a link to the cerebellum. Brain 2001;124(Pt 9):1708–19.
102. Shah SA, Doraiswamy PM, Husain MM, et al. Posterior fossa abnormalities in major depression: a controlled magnetic resonance imaging study. Acta Psychiatr Scand 1992;85:474–9.
103. DelBello MP, Strakowski SM, Zimmerman ME, et al. MRI analysis of the cerebellum in bipolar disorder: a pilot study. Neuropsychopharmacology 1999;21:63–8.
104. Fear, reward, and action. In: Pliszka SR. Neuroscience for the mental health clinician. New York: Guilford Press; 2003:78–89.
105. Heimer L. A new anatomical framework for neuropsychiatric disorders and drug abuse [published erratum appears in Am J Psychiatry 2003;160:2258]. Am J Psychiatry 2003;160:1726–39.
106. Lichter DG, Cummings JL. Introduction and overview. In: Lichter DG, Cummings JL, editors. Frontal-subcortical circuits in psychiatric and neurological disorders. New York: Guilford Press; 2001:1–43.

Copyright 2005 by Turner White Communications Inc., Wayne, PA. All rights reserved.