

Neurobiology of Mood Disorders

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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 compo-

nent,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 D₂ 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

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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 matter³⁷ 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

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.

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.

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 H₁ 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 volume⁵³ 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 implicat-

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.

ed 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

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 states⁵⁹ 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 episodes⁹¹ 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

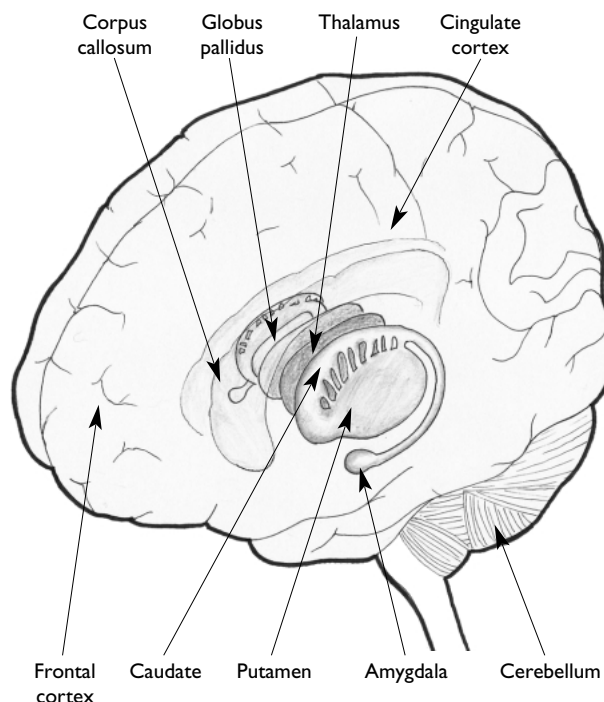


Figure 1. Selected brain structures involved in the neuropathology of mood disorders. The amygdala is the primary structure involved with the processing of emotion and response to the environment. The basal ganglia and thalamus are important structures in the frontal-subcortical circuits.

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

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 regions⁷⁰ 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

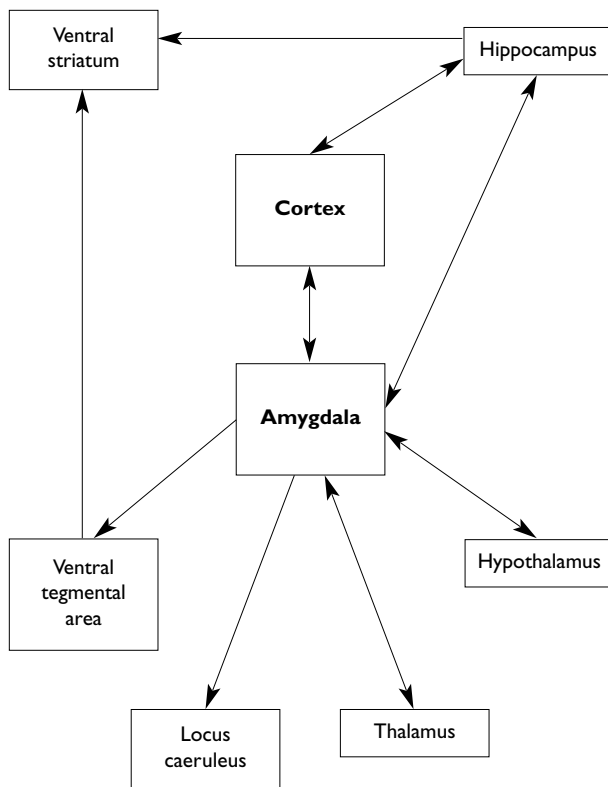


Figure 2. General organizational structure of the limbic circuits and major connections. The amygdala is the structure most involved with formulating emotional response, particularly fear, and determining one's affective perceptions of sensory stimuli. The amygdala receives sensory and body status information 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

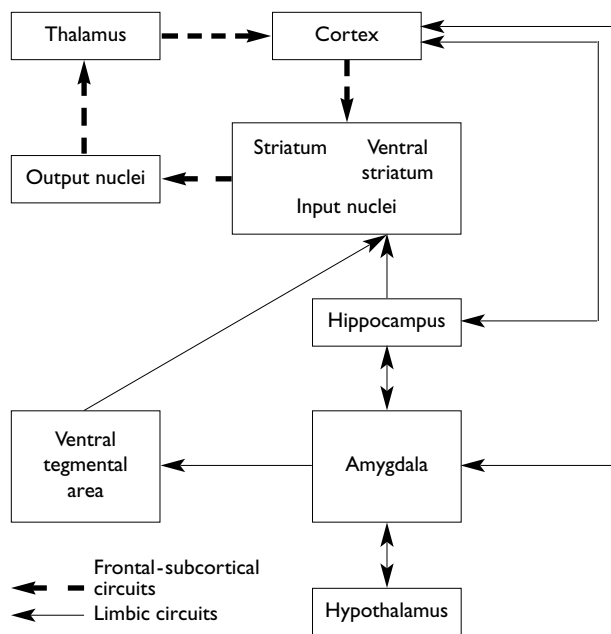


Figure 3. Depiction of the complex relationship between the limbic and frontal-subcortical circuits (FSC; not all connections are shown). Dopamine fibers provide one of the major mechanisms by which the limbic system influences FSC circuits. Afferents from the amygdala to the ventral tegmental area control 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.

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. How-

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.

ever, 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

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