FIGURE 11-37A and B Norepinephrine as an accelerator of serotonin release. Alpha 1 adrenergic receptors are located in the somatodendritic regions of serotonin neurons. When these receptors are unoccupied by norepinephrine, some serotonin is released from the serotonin neuron (A). However, when norepinephrine binds to the alpha 1 receptor this stimulates the serotonin neuron, accelerating release of serotonin (B).
FIGURE 11-38 Norepinephrine bidirectional control of serotonin. Norepinephrine can act as a brake on serotonin release when it binds to alpha 2 receptors at the axon terminal and as an accelerator of serotonin release when it binds to alpha 1 receptors at somatodendritic regions. Thus norepinephrine has bidirectional control of serotonin release.

The original conceptualization was rather simplistic and based on observations that certain drugs which depleted these neurotransmitters could induce depression, and, further, that all effective antidepressants act by boosting one or more of these three monoamine neurotransmitters. Thus the idea was that the “normal” quantity of monoamine neurotransmitters (Figure 11-42A) somehow became depleted — perhaps by an unknown disease process, stress, or drugs (Figure 11-42B) — leading to the symptoms of depression.

Direct evidence for the monoamine hypothesis is still largely lacking. A good deal of effort was expended, especially in the 1960s and 1970s, to identify the theoretically predicted deficiencies of the monoamine neurotransmitters. This effort to date has unfortunately yielded mixed and sometimes confusing results. Some studies suggest that NE metabolites are deficient in some patients with depression, but this has not been uniformly observed. Other studies suggest that the 5HT metabolite 5HIAA (5-hydroxy-indole acetic acid) is
5HT2A Receptors: Reduce Release of DA and NE in Prefrontal Cortex

![Diagram showing 5HT2A receptors regulating norepinephrine and dopamine](image)

FIGURE 11-39 5HT2A receptors regulate norepinephrine and dopamine. Serotonin (5HT) regulates release of norepinephrine (NE) and dopamine (DA) in the prefrontal cortex via 5HT2A receptors located at the somatodendritic ends of NE, DA, and gamma-aminobutyric acid (GABA) neurons. Binding of 5HT at 5HT2A receptors on some NE and DA neurons in the brainstem directly inhibits release of these neurotransmitters into the prefrontal cortex. In addition, binding of 5HT at 5HT2A receptors on some GABA interneurons in the brainstem increases GABA release, which then inhibits NE and DA release.
**FIGURE 11-40 5HT2C receptors regulate norepinephrine and dopamine.** Serotonin (5HT) also regulates release of norepinephrine (NE) and dopamine (DA) in the prefrontal cortex via 5HT2C receptors located on gamma-aminobutyric acid (GABA) interneurons in the brainstem. Binding of 5HT at 5HT2C receptors on these GABA interneurons increases GABA release, which then inhibits NE and DA release from their respective neurons.
5HT2C Receptors: Reduce Release of DA in Nucleus Accumbens

Serotonin (5HT) also regulates release of dopamine (DA) in the nucleus accumbens via 5HT2C receptors on two types of gamma-aminobutyric acid (GABA) neurons. First, stimulation of 5HT2C receptors on GABA interneurons within the brainstem (on the right) causes release of GABA there, which in turn inhibits activity of ascending mesolimbic dopamine projections. This results in reduced DA release in the nucleus accumbens. Second, stimulation of 5HT2C receptors on GABA neurons that project out of the brainstem and into the prefrontal cortex (on the left) leads to inhibition of descending glutamate projections to brainstem dopamine neurons. This, in turn, also leads to reduced DA in the nucleus accumbens.
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FIGURE 11-42A Classic monoamine hypothesis of depression, part 1. According to the classic monoamine hypothesis of depression, when there is a "normal" amount of monoamine neurotransmitter activity, there is no depression present.

FIGURE 11-42B Classic monoamine hypothesis of depression, part 2. The monoamine hypothesis of depression posits that if the "normal" amount of monoamine neurotransmitter activity becomes reduced, depleted, or dysfunctional for some reason, depression may ensue.
receptors upregulate due to lack of monoamines

FIGURE 11-43 Monoamine receptor hypothesis of depression. The monoamine receptor hypothesis of depression extends the classic monoamine hypothesis of depression, positing that deficient activity of monoamine neurotransmitters causes upregulation of postsynaptic monoamine neurotransmitter receptors, and that this leads to depression.

Reduced in the cerebrospinal fluid of depressed patients. On closer examination, however, it has been found that only some of the depressed patients have low CSF 5HIAA, and they tend to be those with impulsive behaviors, such as suicide attempts of a violent nature. Subsequently, it was also reported that CSF 5HIAA is decreased in other populations noted to be subject to violent outbursts or poor impulse control but who were not depressed—namely, patients with antisocial personality disorder who were arsonists and those with borderline personality disorder who engaged in self-destructive acts. Thus, low CSF 5HIAA may be linked more closely with impulse-control problems rather than with depression.

The monoamine hypothesis, monoamine receptors, and gene expression

Because of these and other difficulties with the monoamine hypothesis of depression, the focus of hypotheses for the etiology of depression has shifted from the monoamine neurotransmitters themselves to their receptors and the downstream molecular events that these receptors trigger, including the regulation of gene expression. For example, the neurotransmitter receptor hypothesis of depression posits that an abnormality in the receptors for monoamine neurotransmitters leads to depression (Figure 11-43). Thus, if depletion of monoamine neurotransmitters is the central theme of the monoamine hypothesis of depression (Figure 11-42B), the neurotransmitter receptor hypothesis of depression takes this theme one step further: namely, that the depletion of neurotransmitter causes compensatory upregulation of postsynaptic neurotransmitter receptors (Figure 11-43).
Direct evidence for this is also generally lacking. Postmortem studies do consistently show increased numbers of serotonin 2 receptors in the frontal cortex of patients who commit suicide. Also, some neuroimaging studies have identified abnormalities in serotonin receptors of depressed patients, but this approach has not yet been successful in identifying consistent and replicable molecular lesions in receptors for monoamines in depression.

Thus, there is no clear and convincing evidence that monoamine deficiency accounts for depression; that is, there is no “real” monoamine deficit. Likewise, there is no clear and convincing evidence that abnormalities in monoamine receptors account for depression. Emphasis is now turning to the possibility that in depression there may be a deficiency in downstream signal transduction of the monoamine neurotransmitter and its postsynaptic neuron that is occurring in the presence of normal amounts of neurotransmitter and receptor. Thus the hypothesized molecular problem in depression could lie within the molecular events distal to the receptor, in the signal transduction cascade system and in appropriate gene expression. This is the subject of much current research into the potential molecular basis of affective disorders.

One candidate mechanism that has been proposed as the site of a possible flaw in signal transduction from monoamine receptors is the target gene for brain-derived neurotrophic factor (BDNF) (see discussion in Chapter 2 and illustrations in Figures 2-5 through 2-7 and Figure 2-10). Normally, BDNF sustains the viability of brain neurons; but under stress, the gene for BDNF may be repressed, leading to the atrophy and possible apoptosis of vulnerable neurons in the hippocampus when their neurotrophic factor BDNF is cut off. The idea is that this, in turn, leads to depression and to the consequences of repeated depressive episodes; namely, more and more episodes and less and less responsiveness to treatment. This possibility that hippocampal neurons are decreased in size and impaired in function during depression and anxiety disorders is supported by recent clinical imaging studies showing decreased brain volume of related structures.

This provides a molecular and cellular hypothesis of depression consistent with a mechanism distal to the neurotransmitter receptor and involving an abnormality in gene expression. Thus, stress-induced vulnerability decreases the expression of genes that make neurotrophic factors such as BDNF, which are critical to the survival and function of key neurons. A corollary to this hypothesis is that antidepressants act by reversing this by causing the genes for neurotrophic factors to be activated. The biological consequences of stress are discussed further in Chapter 14, on anxiety disorders.

Although the monoamine hypothesis is obviously an overly simplified notion about depression, it has been very valuable in focusing attention on the three monoamine neurotransmitter systems: norepinephrine, dopamine, and serotonin. This has led to a much better understanding of the physiological functioning of these three neurotransmitters and especially the various mechanisms by which all known antidepressants act to boost neurotransmission at one or more of these three monoamine neurotransmitter systems.

**Symptoms and circuits in depression**

The monoamine hypothesis of depression is now being applied to elucidating how the tri-monoaminergic neurotransmitter system regulates the efficiency of information processing in a wide variety of neuronal circuits that may be responsible for mediating the various symptoms of depression. Obviously numerous symptoms are required for the diagnosis of a major depressive episode (Figure 11-44). Each symptom is hypothetically associated
with inefficient information processing in various brain circuits, with different symptoms topographically localized to specific brain regions (Figure 11-45).

Not only can each of the nine symptoms listed for the diagnosis of a major depressive episode be mapped onto brain circuits that theoretically mediate these symptoms (Figure 11-45), but the hypothetical trimonoaminergic regulation of each of these brain areas can also be mapped onto each brain region they innervate (Figures 11-46 to 11-54). This creates a set of monoamine neurotransmitters that regulate each specific hypothetically malfunctioning brain region. Targeting each region with drugs that act on the relevant neurotransmitters within the trimonoaminergic neurotransmitter system could potentially lead to reduction of each individual symptom experienced by a specific patient by enhancing the efficiency of information processing in malfunctioning circuits for each specific symptom. If successful, this targeting of monoamines in specific brain areas could eliminate symptoms and cause a major depressive episode to go into remission (Figures 11-46 through 11-54).

Generally, the monoaminergic functioning in these circuits in major depressive disorder are represented as being blue, or reduced, consistent with the monoamine hypothesis. However, the more accurate portrayal may be “out of tune” rather than simply deficient. Some brain regions in depression, in fact, have enhanced neuronal activation, and others have reduced neuronal activation. Nevertheless, trimonoaminergic treatments available today for depression all generally boost one or more of the monoamines.

For example, the core symptom of a major depressive episode is depressed mood, thought to be linked to inefficient information processing in the amygdala and in “emotional” areas of the prefrontal cortex, especially the ventromedial prefrontal cortex (VMPFC) and the nearby subgenual area of the anterior cingulate cortex (Figure 11-46). Each of the three monoamine neurotransmitters of the trimonoaminergic neurotransmitter system
Match Each DSM-IV Diagnostic Symptom for a Major Depressive Episode to Hypothetically Malfunctioning Brain Circuits

FIGURE 11-45 Matching depression symptoms to circuits. Alterations in neuronal activity and in the efficiency of information processing within each of the eleven brain regions shown here can lead to symptoms of a major depressive episode. Functionality in each brain region is hypothetically associated with a different constellation of symptoms. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; HY, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum.

innervates these areas; it is therefore not surprising that antidepressants that boost any of these neurotransmitters can improve mood in depression (Figure 11-46).

Apathy or loss of interest is another key symptom of depression and may be more common in elderly patients with depression, even in the absence of depressed mood. How can someone have apathy without depressed mood? The answer is because these symptoms may involve different brain circuits and different neurotransmitters. That is, apathy may involve the prefrontal cortex diffusely, including not only VMPFC but also especially dorsolateral prefrontal cortex as well as the hypothalamic “drive” centers and the nucleus accumbens “pleasure” or interest center (Figure 11-47). Furthermore, whereas deficient dopamine and norepinephrine may regulate these areas and boosting them with antidepressants may help relieve such symptoms associated with these areas, boosting serotonin may actually act to reduce both of these neurotransmitters and make symptoms worse. The mechanisms by which serotonin reduces them are discussed earlier in this chapter and illustrated in Figures 11-39 to 11-41. Thus only NE and DA are shown in Figure 11-47.

Sleep disturbances may be diffusely represented in several brain areas, especially hypothalamus, thalamus, basal forebrain, and diffusely throughout prefrontal cortex, with regulatory input by all three monoamines (Figure 11-48). Fatigue or loss of energy is linked to deficient functioning of NE and DA in prefrontal cortex, especially for mental fatigue, as well as in striatum and nucleus accumbens, especially for physical fatigue (Figure 11-49). Executive dysfunction is fairly well characterized as having localization in the dorsolateral prefrontal cortex (DLPFC) and being regulated mostly by DA and NE (Figure 11-50). Psychomotor symptoms, either agitation or retardation, are linked to motor circuits, especially in the striatum but also in the prefrontal cortex and secondarily perhaps in the cerebellum.
Depressed mood is believed to be linked to inefficient information processing in the amygdala (A) and the ventromedial prefrontal cortex (VMPFC), both of which are innervated by serotoninergic (A), noradrenergic (B), and dopaminergic (C) projections from brainstem nuclei. Reduced, dysfunctional, and inefficient monoaminergic functioning in these regions is depicted here as hypoactive (blue color).
Apathy and depressed mood are often considered similar symptoms, but they are hypothetically regulated by different brain circuits. Apathy is believed to be related to inefficient information processing (depicted here as blue or hypoactive) diffusely through the prefrontal cortex (PFC) as well as in hypothalamic centers (Hy) and the nucleus accumbens (NA). These functions within the prefrontal cortex and hypothalamus are thought to be regulated in part by noradrenergic neurons that project there (A), while within prefrontal cortex, hypothalamus, and nucleus accumbens these functions are also thought to be regulated by dopaminergic projections (B).

Changes in weight and appetite, either increased or decreased, have important hypothalamic and serotonergic components to their regulation (Figure 11-52). Suicidal ideation (Figure 11-53) as well as feelings of guilt and worthlessness (Figure 11-54) all have profound connections to serotonin and to circuits connecting to amygdala and emotional regulatory areas of the prefrontal cortex, including the ventromedial prefrontal cortex and perhaps the orbitofrontal cortex.

Many of the mood-related symptoms of depression can be categorized as having either too little positive affect or too much negative affect (Figure 11-55). This idea is linked to the fact that there are diffuse anatomic connections of the trimonoaminergic neurotransmitter system throughout the brain, with diffuse dopamine dysfunction in this system.
Sleep disturbances are believed to be linked to inefficient information processing in the hypothalamus (Hy), thalamus (T), basal forebrain (BF), and diffusely in the prefrontal cortex (PFC), depicted here by the blue color representing hypoactivity. All of these brain regions are regulated by serotonergic (A), noradrenergic (B), and dopaminergic (C) projections from brainstem nuclei.
Fatigue or loss of energy is linked to inefficient information processing in several brain regions as well as in the spinal cord, shown here as hypoactivity (blue color). Specifically, mental fatigue is related to deficient noradrenergic functioning in the prefrontal cortex (PFC), while physical fatigue is related to deficient noradrenergic functioning in descending spinal cord (SC) projections (A). Dopamine also plays a role in fatigue, with deficient dopaminergic functioning in the PFC related to mental fatigue and deficient dopaminergic functioning in the striatum (S), nucleus accumbens (NA), hypothalamus (Hy), and SC related to physical fatigue (B).

Driving predominantly the reduction of positive affect, with diffuse serotonin dysfunction driving predominantly the increase in negative affect, and with norepinephrine dysfunction being involved in both. Thus reduced positive affect includes such symptoms as depressed mood but also loss of happiness, joy, interest, pleasure, alertness, energy, enthusiasm, and self-confidence (Figure 11-55, on the left). Enhancing dopamine function and possibly also norepinephrine function may improve information processing in the circuits mediating this cluster of symptoms. On the other hand, increased negative affect includes not only depressed mood but also guilt, disgust, fear, anxiety, hostility, irritability, and loneliness (Figure 11-55, on the right). The enhancement of serotonin function and possibly also norepinephrine function may improve information processing in the circuits that...
Executive dysfunction is associated with inefficient information processing (depicted here as blue or hypoactive), specifically in the dorsolateral prefrontal cortex (DLPFC), which receives important regulatory projections from both noradrenergic (A) and dopaminergic (B) neurons.

Symptoms and circuits in mania

The same general paradigm of trimonoaminergic neurotransmitter system regulation of the efficiency of information processing in specific brain circuits can be applied to mania as well as depression, although this is frequently thought to be in the opposite direction and in some overlapping but some different brain regions compared to depression. The numerous hypothetically mediate this cluster of symptoms. Patients with symptoms of both clusters may require triple-action treatments that boost all three of the trimonoamine neurotransmitters.
Psychomotor agitation or retardation may be related to inefficient information processing in multiple brain regions innervated by serotonergic (A), noradrenergic (B), and/or dopaminergic (C) projections. These regions include the cerebellum, which receives serotonergic and noradrenergic projections, the striatum and nucleus accumbens, which receive serotonergic and dopaminergic projections, and the prefrontal cortex (PFC), which receives projections from all three monoamines. In this figure, the monoaminergic functioning is depicted as hypoactive (blue color).
weight/appetite changes

**FIGURE 11-52 Weight and appetite circuit.** Appetite and weight are mediated in large part by the hypothalamus (Hy), which receives serotonergic projections. Thus, any changes in weight or appetite as a symptom of depression may be related in part to serotonergic control of the hypothalamus (shown here as blue to denote hypoactivity).

**FIGURE 11-53 Suicide circuit.** Suicidal ideation is believed to be regulated by inefficient information processing (shown here in blue for hypoactivity) in brain regions associated with emotionality, such as the amygdala (A), ventromedial prefrontal cortex (VMPFC), and orbital frontal cortex (OFC). These brain regions receive important regulatory control for suicidality from serotonergic projections.
FIGURE 11-54 Guilt/worthlessness circuit. As with suicidal ideation, feelings of guilt or worthlessness are regulated by "emotional" brain regions such as the amygdala (A) and ventromedial prefrontal cortex (VMPFC), which are innervated by important serotonergic regulatory projections. Inefficient information processing in these regions (depicted here as blue or hypoactive) may cause these symptoms to occur.

FIGURE 11-55 Positive and negative affect. Mood-related symptoms of depression can be characterized by their affective expression— that is, whether they cause a reduction in positive affect or an increase in negative affect. Symptoms related to reduced positive affect include depressed mood; loss of happiness, interest, or pleasure; loss of energy or enthusiasm; decreased alertness; and decreased self-confidence. Reduced positive affect may be hypothetically related to dopaminergic dysfunction, with a possible role of noradrenergic dysfunction as well. Symptoms associated with increased negative affect include depressed mood, guilt, disgust, fear, anxiety, hostility, irritability, and loneliness. Increased negative affect may be linked hypothetically to serotonergic dysfunction and perhaps also noradrenergic dysfunction.
DSM-IV Symptom Dimensions of a Manic Episode

![Diagram showing symptoms of a manic episode]

FIGURE 11-56 DSM-IV symptoms of mania. According to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), a manic episode consists of either elevated/expansive mood or irritable mood. In addition, at least three of the following must be present (four if mood is irritable): inflated self-esteem/grandiosity, increased goal-directed activity or agitation, risk taking, decreased need for sleep, distractibility, pressured speech, and racing thoughts.

Match Each DSM-IV Diagnostic Symptom for a Manic Episode to Hypothetically Malfunctioning Brain Circuits

![Diagram matching mania symptoms to circuits]

FIGURE 11-57 Matching mania symptoms to circuits. Alterations in neurotransmission within each of the eleven brain regions shown here can be hypothetically linked to the various symptoms of a manic episode. Functionality in each brain region may be associated with a different constellation of symptoms. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; HY, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum.
Elevated/expansive or irritable mood may be hypothetically linked to inefficient information processing (depicted here in red to denote hyperactivity) in the amygdala (A), ventromedial prefrontal cortex (VMPFC), and orbital frontal cortex (OFC), all of which are innervated by serotonergic (A), noradrenergic (B), and dopaminergic (C) projections from brainstem nuclei.
Symptoms such as grandiosity, flight of ideas, and racing thoughts may be hypothetically linked to inefficient information processing (depicted here in red as hyperactivity) in the same brain regions associated with positive symptoms of psychosis (e.g., nucleus accumbens (NA)). Other manic symptoms, such as risk taking and pressured speech, may be manifestations of poor impulse control and thus regulated by the orbital frontal cortex (OFC). Other areas of the prefrontal cortex, such as the dorsolateral prefrontal cortex (DLPFC) and ventromedial prefrontal cortex (VMPFC), may also be involved in these symptoms. Regulation of these areas of presumed inefficient information processing in prefrontal cortex include serotonergic (A), noradrenergic (B), and dopaminergic (C) projections, while the nucleus accumbens is innervated by serotonergic (A) and dopaminergic (C) projections.

FIGURE 11-59A, B, and C Mania symptom circuits.
Although sleep disturbances manifest themselves differently in a major depressive versus a manic episode (i.e., insomnia or hypersomnia versus decreased subjective need for sleep), they may still be regulated by many of the same brain regions. Thus decreased need for sleep may be linked to inefficient information processing in the hypothalamus (Hy), thalamus (T), and basal forebrain (BF), depicted here by the red color representing hyperactivity. All of these brain regions are innervated by serotonergic (A), noradrenergic (B), and dopaminergic (C) projections from brainstem nuclei.
Cognitive problems in mania, such as distractibility or poor concentration, may be associated with aberrant information processing (depicted here as red or hyperactive) specifically in the dorsolateral prefrontal cortex (DLPFC), which receives important regulatory projections from both noradrenergic (A) and dopaminergic (B) neurons.

Generally, the monoaminergic functioning in these circuits in mania is represented as being red, or hyperactive, and thus essentially the opposite of the malfunctioning hypothesized for depression (see Figures 11-46 through 11-54). As for depression, however, the more accurate portrayal may be "out of tune" rather than simply excessive, especially since some patients can simultaneously have both manic and depressed symptoms. Generally,
however, treatments of mania either reduce or stabilize trimonoaminergic regulation of circuits associated with symptoms of mania.

Just as shown for depression, each of the nine symptoms listed for the diagnosis of mania (Figure 11-56) can also be mapped onto brain circuits that theoretically mediate these symptoms (Figure 11-57), and the hypothetical trimonoaminergic regulation of each of these brain areas can be mapped onto each of the brain regions they innervate as well (Figures 11-58 through 11-62). Targeting each affected region with drugs that act on the relevant neurotransmitters within the trimonoaminergic neurotransmitter system could potentially lead to reduction of each individual manic symptom experienced by a specific
Key Genes That Hypothetically Regulate Mood Networks: Convergence Upon Trimonoamine Neurotransmitter System

![Brain diagram with key genes and neurotransmitter systems](image)

**FIGURE 11-63** Key genes that hypothetically regulate mood networks. Several key genes that code for proteins that regulate mood networks are shown here. Many of these genes converge on the trimonoaminergic neurotransmitter system, supporting the role of these three neurotransmitters — serotonin, norepinephrine, and dopamine — in both the symptoms and treatments of mood disorders.

Patient by enhancing the efficiency of information processing in malfunctioning circuits for each specific symptom. If successful, this targeting of monoamines in specific brain areas could eliminate manic symptoms and cause a manic episode to remit (Figures 11-58 through 11-62).

For example, the core symptoms of a manic episode are elevated, expansive, or irritable mood (Figure 11-58). Thus, patients may have some elements of enhanced negative affect, such as irritability and dysphoria, as experienced by some depressed patients (Figure 11-55). As is the case for depressed mood, these other moods are hypothetically linked to the amygdala, ventromedial prefrontal cortex, and orbitofrontal cortex, with regulation by all three monoamine neurotransmitters (Figure 11-58).

On the other hand, symptoms of inflated self-esteem, grandiosity, flight of ideas, and racing thoughts may be linked to the psychotic symptoms discussed in Chapter 10 and thus to limbic areas such as nucleus accumbens, with risk taking and pressured speech linked to poor impulse control and perhaps therefore to orbitofrontal cortex (Figure 11-59). Sleep disturbance as a symptom of a manic episode (Figure 11-60) may be linked to many of the same areas as sleep disturbance as a symptom of depression (Figure 11-48), although the symptom in mania is not really insomnia but rather a decreased subjective need for sleep. Similarly, distractibility and problems concentrating as symptoms of a manic episode (Figure 11-61) are likely associated with the same brain area as that associated with executive dysfunction such as problems concentrating in a major depressive episode (Figure 11-50) — namely, the dorsolateral prefrontal cortex. Increased goal-directed activity or agitation may be linked to the striatum in mania (Figure 11-62).
As the reader can see, there is considerable overlap between mania and depression, and common symptoms are hypothetically mediated by the same circuits. Obviously this is a simplistic and reductionistic approach to mapping symptoms of mania and depression; many brain areas are involved, since each brain area is linked to many others. Nevertheless, this idea of constructing a diagnosis, then deconstructing it into its symptom components, and then matching each symptom to a hypothetically malfunctioning brain circuit can be useful in choosing treatments for individual patients. This approach is sometimes called symptom-based treatment selection and combination and is discussed in much further detail in Chapter 12, on antidepressants, and in Chapter 13, on mood stabilizers.

**Genes and neuroimaging in mood disorders**

Many of the issues in identifying gene abnormalities in mood disorders are the same as those discussed in Chapter 9 for identifying gene abnormalities in schizophrenia. In fact, many of the same genetic abnormalities associated with schizophrenia may apply in part to mood...
Depressed Patients May Be More Responsive to Induction of Sadness Than to Induction of Happiness

FIGURE 11-65 Depressed patient’s neuronal response to induced sadness versus happiness. Emotional symptoms such as sadness or happiness are regulated by the ventromedial prefrontal cortex (VMPFC) and the amygdala, two regions in which activity is high in the resting state of depressed patients (left). Interestingly, provocative tests in which these emotions are induced show that neuronal activity in the amygdala is overreactive to induced sadness (bottom right) but underreactive to induced happiness (top right).

Disorders, especially bipolar disorder (see Figures 9-53 through 9-58). The confluence of genetic risk plus environmental stressors is thought to be the same general paradigm for mood disorders, as previously discussed for schizophrenia. The role of stress and genes is also discussed in Chapter 14, on anxiety. Several of the key genes that hypothetically regulate mood networks not surprisingly all converge on the trimonoamine neurotransmitter system (Figure 11-63). How these genes influence neurodevelopment, synaptic plasticity, neuronal connectivity, and the efficiency of neuronal information processing in mood disorders is currently under intense investigation.

In terms of neuroimaging mood disorders, there is general agreement that in depression, the dorsolateral prefrontal cortex, associated with cognitive symptoms, may have reduced activity, and the amygdala and ventromedial prefrontal cortex, associated with various emotional symptoms including depressed mood, may have increased activity (Figure 11-64). Furthermore, provocative testing of patients with mood disorders may provide some insight into the malfunctioning of brain circuits that are exposed to environmental input and required to process it. For example, some studies of depressed patients show that their
Manic Patients Do Not Activate Inhibitory Orbitofrontal Circuits in Response to a No-Go Task

![Diagram of brain activity in manic patients](image)

**FIGURE 11-66** Manic patient's neuronal response to no-go task. Impulsive symptoms of mania, such as risk taking and pressured speech, are related to activity in the orbital frontal cortex (OFC). Neuroimaging data show that this brain region is hypoactive in manic (bottom right) versus normal (bottom left) individuals during the no-go task, which is designed to test response inhibition.

Neuronal circuits at the level of the amygdala and ventromedial prefrontal cortex are overly reactive to induced sadness but underreactive to induced happiness (Figure 11-65). On the other hand, imaging the orbitofrontal cortex of manic patients shows that they fail to appropriately activate this brain region in a test that requires them to suppress a response, suggesting problems with impulsivity associated with mania and with this specific brain region (Figure 11-66). In general, these neuroimaging findings support the mapping of symptoms to brain regions discussed earlier in this chapter, but much further work is currently in progress and must be completed before the results of neuroimaging can be applied to diagnostic or therapeutic decision making in clinical practice.

**Summary**

This chapter has described the mood disorders, including those across the bipolar spectrum. For prognostic and treatment purposes, it is increasingly important to be able to distinguish unipolar depression from bipolar spectrum depression. Although mood
disorders are indeed disorders of mood, they are much more, and several different symp-
toms in addition to a mood symptom are required to make a diagnosis of a major depressive 
episode or a manic episode. Each symptom can be matched to a hypothetically malfunc-
tioning neuronal circuit. The monoamine hypothesis of depression suggests that dysfunc-
tion— generally due to underactivity— of one or more of the three monoamines DA, NE, or 5HT 
of the trimonoaminergic neurotransmitter system may be linked to symptoms in major 
depression. Boosting one or more of the monoamines in specific brain regions may improve 
the efficiency of information processing there and reduce the symptom caused by that area’s 
malfunctioning. Other brain areas associated with the symptoms of a manic episode can 
similarly be mapped to various hypothetically malfunctioning brain circuits. Understanding 
the localization of symptoms in circuits—as well as the neurotransmitters that regulate these 
circuits in different brain regions— can set the stage for choosing and combining treatments 
for each individual symptom of a mood disorder, with the goal being to reduce all symptoms 
and bring about remission.