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Depressive and Bipolar Disorders

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Mood Disorders

Consider the case of David, a 24-year-old male who sought neuropsychological testing to assess for attention deficit hyperactivity disorder (ADHD).

David had been taking classes at a local university for the past 4 years to complete his degree. He wanted to be assessed for ADHD because he was experiencing significant difficulties sustaining and paying attention in his classes, and his grades began to suffer. He failed his classes one semester and was placed on academic probation.

Additionally, David was running his own Internet advertising business while attending school. He reported that he was able to keep the business running, but that he felt it was suffering due to his current state of disorganization. He was unable to arrive to meetings on time, took poor notes, and had considerable difficulty keeping the business organized. As a result, he was in debt and could not properly manage his finances.

Although many elements of David's story are common in individuals with ADHD, they are also familiar to many people who suffer from severe depression. During David's assessment, he was given a diagnostic interview as well as the Beck Depression Inventory (BDI), a 21-item self-report of depressive symptoms. David reported depressed mood, feelings of hopelessness about his future, irritability, guilt about his failing business and poor academic performance, marked fatigue and sluggishness, anhedonia, and severe sleep disturbance (marked insomnia, sleep continuity disturbance, and early morning awakenings). His symptoms were persistent and severe enough to meet the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5; American Psychological Association, 2013) criteria for a major depressive episode, and his high score on the BDI (43) indicated that this episode was particularly severe. Moreover, David also reported substantial symptoms of anxiety and worry, such as feelings of dread, numbness, hot and cold sweats, shortness of breath, and heart palpitations. Anxiety symptoms are often comorbid in an episode of major depressive disorder, and can contribute to the overall impairment of the episode.

Although David had been aware that his mood was lower than he would like it to be, it was not his mood, but rather his inability to keep himself organized, make everyday decisions, or focus on his work that was driving him to seek an assessment for ADHD, which he suspected was the root of his day-to-day difficulties. David was given a battery of neuropsychological tests, in addition to diagnostic interviews. Although the results of these assessments were indicative of impairments in attention and concentration, the severity of David's depression and anxiety made it nearly impossible to assign an unequivocal diagnosis of ADHD. Instead, the evaluator recommended that David first seek treatment for his depression and anxiety, as she hypothesized that his attention and concentration symptoms would improve as a result.

David's story is not an uncommon one in clinical settings. Many individuals with moderate to severe depression experience marked impairments in their ability to do their jobs, perform well in school, and stay on top of household chores. However, major depressive disorder is often responsive to treatment either with psychotherapy, pharmacotherapy, or their combination, and many see a restoration of their general functioning following a targeted treatment regimen.

We are all familiar, at least casually, with what depression is like. We have all experienced occasional periods of sadness, where nothing seems worth doing, we become tired and slowed down, and our lives are no longer fun.

Some have also experienced the opposite state, when we feel on top of the world, excited and reckless, and we become hyperactive and think that we can accomplish anything. In other words, *depression* and *mania*, in mild and temporary forms, are part of everyday existence. For some people, however, these mood swings become so prolonged and extreme that the person's life is seriously disrupted. These conditions are known as *mood disorders* or *affective disorders*.

Mood disorders have been recognized as clinical entities for over 2000 years. Indeed, Hippocrates described both depression and mania in detail in the fourth century B.C.E. As early as the first century C.E., the Greek physician Aretaeus observed that manic and depressive behaviors sometimes occurred in the same person and seemed to stem from a single disorder. Although they have been studied for centuries, as yet, there are no completely satisfactory explanations for the puzzling features of mood disorders. In this chapter, we first describe the mood disorders as well as their diagnosis, symptoms, dimensions, and risk factors. Then, we review what is known about the causes and treatment of mood disorders from various theoretical perspectives.

Depressive and Manic Episodes

Typically, mood disorders are episodic. Within days, weeks, or months, a person who has been functioning normally is plunged into despair or becomes euphoric. Once the episode runs its course, the person may return to normal or near-normal functioning, though he or she is likely to have recurrences of mood disturbance. The severity, duration, and nature of the episode (whether depressive or manic) determine the diagnosis. Below are the typical features of depressive and manic episodes.

Major Depressive Episode Onset of a *major depressive episode* is usually gradual, occurring over a period of several weeks or months, and the episode typically lasts several months and then ends, as it began, gradually (Coryell et al., 1994). Major depressive episodes affect mood, motivation, thinking, somatic, and motor functioning. The characteristic features of a major depressive episode are as follows (see Table 11.1 for the DSM-5 diagnostic criteria):

1. *Depressed mood:* Almost all depressed adults report some sadness, ranging from mild melancholy to total hopelessness. Mildly or moderately depressed people may have crying spells; severely depressed individuals often say they feel like crying but cannot. Deeply depressed people see no way that they or anyone else can help them—the helplessness–hopelessness syndrome.
2. *Loss of pleasure or interest in usual activities:* Anhedonia, the loss of pleasure or interest in one's usual activities, is the other most common characteristic of a major depressive episode. Even emotional responses to pleasant stimuli are diminished during a major depressive episode (Sloan, Strauss, & Wisner, 2001).
3. *Disturbance of appetite:* Most depressed people have poor appetite and lose weight; however, a minority react by eating more and putting on weight. Whichever type of weight change, the same change tends to occur with each depressive episode (Kendler et al., 1996).
4. *Sleep disturbances:* Insomnia is an extremely common feature of depression and can take one or more of three forms. Depressed people may have trouble falling asleep initially, or may awaken repeatedly throughout the night, or may wake up too early in the morning and be unable to fall back to sleep. However, like eating, sleep may increase rather than decrease, with the depressed person sleeping 15 hours a day or more. Depressed individuals who exhibit excessive sleeping are usually the same ones who eat excessively (Kendler et al., 1996).
5. *Psychomotor retardation or agitation:* In retarded depression, the most common psychomotor pattern, the depressed person is fatigued, movement is slow and deliberate, posture is stooped, and speech is low and halting, with long pauses before answering. In severe cases, individuals may fall into a mute stupor. Some evidence suggests that the symptom of psychomotor retardation is related to low presynaptic dopamine levels (Paillere et al., 2001). Less frequently, in agitated depression, the person shows incessant activity and restlessness—hand wringing and pacing.
6. *Loss of energy:* The depressed person usually exhibits a sharply reduced energy level and may feel exhausted all the time.
7. *Feelings of worthlessness and guilt:* Depressed people see themselves as deficient in whatever attributes they value most: intelligence, beauty, popularity. These feelings of worthlessness are often accompanied by a profound sense of guilt. Depressed individuals believe that any problem is their fault.
8. *Difficulties in thinking:* As in David's case, depressed people have trouble concentrating, remembering, and making decisions, even about everyday matters (what to wear, etc.). The harder a mental task, the more difficulty they have (Hartlage, Alloy, Vasquez, & Dykman, 1993).
9. *Recurring thoughts of death or suicide:* Many depressed people have recurrent thoughts of death and suicide. Often, they say that they (and everyone else) would be better off if they were dead.

Manic Episode A typical *manic episode* begins relatively suddenly, over a few days, and is usually shorter than a

TABLE 11.1
Changes from DSM-IV-TR to DSM-5 Criteria for Manic, Hypomanic, Depressive, and Mixed Episodes

Condition	Criteria Description
Manic Episode	A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, **and abnormally and persistently increased goal-directed activity or energy**, lasting at least 1 week (or any duration if hospitalization is necessary). B. During the period of mood disturbance **and increased energy or activity**, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree **and represent a noticeable change from usual behavior**: 1. inflated self-esteem or grandiosity 2. decreased need for sleep 3. more talkative than usual or pressure to keep talking 4. flight of ideas or subjective experience that thoughts are racing 5. distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli) 6. increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation 7. excessive involvement in activities that a high potential for painful consequences C. The symptoms do not meet criteria for a Mixed Episode D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning, or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features. E. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism). Manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar I Disorder.
Hypomanic Episode	A. A distinct period of persistently elevated, expansive, or irritable mood **and abnormally and persistently increased activity or energy**, lasting throughout at least 4 days, that is clearly different from the usual non-depressed mood **and present most of the day, nearly every day**. B. During the period of mood disturbance **and increased energy and activity**, three (or more) of the following symptoms have persisted (four if the mood is only irritable), **represent a noticeable change from usual behavior**, and have been present to a significant degree: 1. inflated self-esteem or grandiosity 2. decreased need for sleep 3. more talkative than usual or pressure to keep talking 4. flight of ideas or subjective experience that thoughts are racing 5. distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli) 6. increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation 7. excessive involvement in pleasurable activities that have a high potential for painful consequences C. The episode is associated with an unequivocal change in functioning that is characteristic of the person when not symptomatic D. The disturbance in mood and the change in functioning are observable by others E. The episode is not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalization, and there are no psychotic features. F. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism). Hypomanic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, light therapy) should not count toward a diagnosis of Bipolar II Disorder. **Note: A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.**
Major Depressive Episode	A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. 1. depressed mood, most of the day, nearly every day, as indicated by subjective report 2. markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day. 3. significant weight loss when not dieting, or weight gain, or decrease or increase in appetite nearly every day. 4. insomnia or hypersomnia nearly every day 5. psychomotor agitation or retardation nearly every day (observable by others) 6. fatigue or loss of energy nearly every day 7. feelings of worthlessness or excessive or inappropriate guilt 8. diminished ability to think or concentrate, or indecisiveness, nearly every day 9. recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or plan

	B.	The symptoms do not meet criteria for a Mixed Episode
	C.	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
	D.	The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
	E.	The symptoms are not better accounted for by bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.
Mixed Episode	A.	The criteria are met for both a Manic Episode and for a Major Depressive Episode (except for duration) every day during at least a 1-week period.
	B.	The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
	C.	The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition (e.g., hyperthyroidism).

Note: Bold text indicates additions to diagnostic criteria in the DSM 5. Strikethrough text indicates diagnostic criteria that have been deleted in the DSM 5.

depressive episode, lasting from several days to several months. The features of a manic episode are as follows (see Table 11.1 for the DSM-5 diagnostic criteria):

1. *Elevated, expansive, or irritable mood accompanied by abnormally and persistently increased goal-directed activity or energy*: Typically, people in a manic episode feel "high" and on top of the world and have limitless enthusiasm for whatever they are doing. This expansiveness is often mixed with irritability when someone tries to interfere with their behavior. In some cases, irritability is the manic person's dominant mood, with euphoria either intermittent or simply absent. The elevated or irritable mood is accompanied by super-charged energy and increased goal-directed activity across multiple domains.
2. *Inflated self-esteem*: People with mania believe they have highly important plans, and special talents and abilities. They tend to see themselves as extremely attractive, powerful, and capable of great achievements even if they have no such aptitude. They may begin composing symphonies, designing nuclear weapons, or calling the White House with ideas on how to run the country.
3. *Sleeplessness*: Manic episodes are almost always marked by a decreased need for sleep. Manic individuals may sleep only 2 or 3 hours a night, but have twice as much energy as others.
4. *Talkativeness*: People with mania tend to talk loudly, rapidly, and constantly. Their speech is often full of puns and jokes that they alone find funny.
5. *Flight of ideas*: Manic individuals' speech often shifts rapidly from topic to topic. They often have racing thoughts; this may be why they speak so rapidly—to keep up with their ideas.
6. *Distractibility*: Manic individuals are easily distracted. Their attention is frequently pulled by irrelevant and unimportant aspects of the environment.
7. *Hyperactivity*: The expansive mood is usually accompanied by restlessness and increased goal-directed activity—physical, social, occupational, and often sexual.
8. *Reckless behavior*: The euphoria and grandiose self-image of manic people often lead them to impulsive, reckless actions: shopping sprees, reckless driving, careless business investments, sexual indiscretions, and so on. They may impulsively call friends in the middle of the night or spend the family savings on a new Porsche.

A hypomanic episode is briefer and less severe than a manic episode, and does not require impairment, but has similar symptoms as a manic episode. A hypomanic episode does, however, require a change in functioning and must be observable by others. When a person meets criteria for major depression and manic or hypomanic episodes simultaneously (e.g., exhibits manic hyperactivity and grandiosity, but also cries and is suicidal), it's called a mixed episode. Mixed episodes are not uncommon (Vieta & Morralla, 2010) and are proposed as a specifier of mood disorders in DSM-5.

Mood Disorder Syndromes

Major Depressive Disorder People who experience one or more major depressive episodes, with no mania or hypomania, have, according to the DSM, major depressive disorder (MDD). The prevalence of this disorder during any given month is close to 4% of men, and 6% of women. The lifetime risk is about 20% (Kessler & Wong, 2009). Major depression is predicted to be the leading cause of disability and premature death worldwide in the 21st century (World Health Organization, 2003). Depression leads to more office visits than any other medical problem except hypertension and greater impairment—more workdays lost, more time in bed—than chronic medical conditions, such as diabetes or heart disease (Druss, Rosenheck, & Sledge, 2000; Wells & Sherbourne, 1999). Further, although there are effective treatments for depression, most people with major depression do not receive adequate treatment (Young, Klap, Sherbourne, & Wells, 2001). Moreover, each successive generation born since World War II has shown higher rates of depression

(Burke, Burke, Rae, & Regier, 1991; Compton, Conway, Stinson, & Grant, 2006; Klerman, 1988). According to some experts, we are in an "age of depression."

Course Major depression is a highly recurrent disorder, with about 80% of all people with first onset of major depression experiencing at least one recurrence (Boland & Keller, 2009). The more previous episodes, the younger the person was at first onset, female gender, family history of depression, the more stressful life events endured recently, the less social support the person received, and the more negative cognitions the individual has, the greater the likelihood of recurrence (Belsher & Costello, 1988; Burcusa & Iacono, 2007). Over a lifetime, the median number of episodes per patient is four, with a median duration of 4½ months per episode (Judd, 1997; Solomon et al., 1997).

The course of recurrent depression varies considerably. Following a depressive episode, some people return to their level of functioning prior to the onset of the disorder, whereas others still show serious impairment in job status, income, marital adjustment, social relationships, and recreational activities 10 years after the episode (Judd et al., 2000). Depression also affects the immune system, leaving people more susceptible to illness and death (Raison & Miller, 2012). Thus, it is difficult for people recovering from a depressive episode to resume their former lives. Indeed, research on "stress generation" indicates that the symptoms and behaviors characteristic of a depressive episode actually generate stressful life events, which in turn can maintain the depression and produce a cycle of chronic stress and impairment (Daley et al., 1997; Liu & Alloy, 2010).

The early course or prodrome of depression (early symptoms or signs of an impending episode) has also garnered attention (Jackson, Cavanaugh, & Scott, 2003; Iacoviello, Alloy, Abramson, & Choi, 2010). Certain symptoms, such as sad mood, anhedonia, hopelessness, difficulty concentrating, worrying/brooding, decreased self-esteem, and irritability, are more likely to be present among individuals entering a depressive episode than among demographically similar individuals who did not develop an episode. In addition, the durations of prodromal and residual (symptoms still present as an episode is remitting) phases are correlated, the prodromal and residual symptom profiles are quite similar, and the order of symptom onset during the prodrome is negatively correlated with the order of symptom remission (Iacoviello et al., 2010).

Groups at Risk of Depression Although depression can strike anyone at any time, some groups are especially vulnerable to depression. Research has shown that Hispanic youth, and especially Hispanic girls, tend to have higher rates of depressive symptoms than white or African American youth (Twenge & Nolen-Hoeksema, 2002; McLaughlin, Hilt, & Nolen-Hoeksema, 2007). Some of these differences, however, can be accounted for by controlling for parental education level as well as differences in poverty and perceived support at home and at school (Kennard, Mahtani, Hughes, Patel, & Emslie, 2006; Mikolajczyk, Bredehorst, Khelaifat, Maier, & Maxwell, 2007). Never married and formerly married individuals have higher depressive symptoms than those who are married (Mirowsky & Ross, 2003; Turner & Lloyd, 1999). In addition, later-born cohorts have a higher lifetime prevalence of depression (Kessler et al., 2003), which has led to the popular belief that there is currently a depression "epidemic" among today's youth. A large meta-analysis has shown, however, that when concurrent assessment rather than retrospective recall is used, there is no evidence for an increased prevalence of child or adolescent depression over the past 30 years (Costello, Erkanli, & Angold, 2006). At the other end of the age spectrum, comorbid conditions associated with aging rather than aging itself may be responsible for the increase in depressive symptoms seen with age (Snowdon, 2001). According to Nguyen and Zonderman (2006), rates of depression remain relatively stable across most of the adult lifespan (ages 25–70) and increase thereafter.

One of the most consistent findings in depression research is the gender difference in rates of depression. Epidemiological studies conducted in the United States and some European countries have shown that women are twice as likely to develop depression as men (Angst et al., 2002; Kuehner, 2003). In addition, the dramatic gender difference in depression rates in women first emerges during adolescence (Hankin & Abramson, 2001; Nolen-Hoeksema, 2001) and lasts through adulthood. Prior to adolescence, boys and girls tend to have similar rates of depression and some research has shown that boys might be at an even higher risk for developing depression (Twenge & Nolen-Hoeksema, 2002). These differences in prevalence rates of depression are due to women having a higher risk of first onset, not a difference in the persistence or recurrence of the depressive episodes (Kessler, 2003). There are some cultural groups, such as the Old Order Amish and Orthodox Jews, that serve as intriguing exceptions to these widespread findings (Angst et al., 2002; Piccinelli & Wilkinson, 2000). Depression rates for women in these groups may be lower because these groups' cultural norms reduce the sexual objectification of girls in adolescence (Hyde, Mezulis, & Abramson, 2008).

Many factors have been implicated in the gender difference in depression rates across the lifespan. Adolescent girls might not welcome the physical changes that accompany puberty as much as boys do, and research has shown that this "body dissatisfaction" is often associated with depressive symptoms (Siegel, Yancey, Aneshensel, & Schuler, 1999; Hankin & Abramson, 2001). Researchers also have identified several psychological factors that contribute to women's vulnerability to developing depression. One is women's interpersonal orientation. It has been suggested

that women tend to derive more of their self-worth from their relationships than men (Cyranowski, Frank, Young, & Shear, 2000). Adolescent girls generally score higher than boys on measures of need for social approval and reassurance seeking, which puts them at higher risk for developing depressive symptoms (Rudolph & Conley, 2005). Women's greater interpersonal orientation makes them more susceptible to experiencing more interpersonal stressors, which have been associated with depression (Hammen, 2003; Hamilton, Stange et al., 2013).

Although individuals can respond to sad mood in a variety of ways, rumination is especially harmful. Rumination involves responding to one's sad mood in a passive manner by repeatedly dwelling on the causes and symptoms of one's depressive mood rather than taking active steps to change one's mood (Nolen-Hoeksema, 1991). Women tend to ruminate more than men in response to sad mood, and controlling for the gender difference in rumination makes the gender difference in depression disappear (Nolen-Hoeksema & Jackson, 2001; Nolen-Hoeksema, Larson, & Grayson, 1999).

Along with biological and psychological factors, social factors also play a role in explaining the higher rates of depression in women. Women experience higher levels of sexual and physical abuse than men, which put them at a higher risk for developing depression across their lifetime (Weiss, Longhurst, & Mazure, 1999; Kendler, Gardner, & Prescott, 2002). Childhood sexual abuse has been found to be an especially strong predictor of development of future psychopathology, including depression (Kendler, Kuhn, & Prescott, 2004).

No single factor is implicated in the disparity in rates of depression among men and women. Hyde, Mezulis, and Abramson (2008) proposed a model that suggests that women have a variety of vulnerability factors that interact with new stressors that emerge in adolescence to produce the gender gap in depression.

Bipolar Disorder Whereas major depression is confined to depressive episodes, bipolar disorder typically involves both manic or hypomanic and depressive episodes. Some individuals have a manic episode—or a series of such episodes—with no depressive episodes. Such cases, although they involve only one "pole," are still classified as bipolar disorder, because, aside from the absence of depressive episodes, they resemble the classic bipolar disorder. Some researchers suspect that they are simply cases of insufficient follow-up for depressive episodes. Alternatively, some individuals have both depressive and hypomanic, rather than fully manic, episodes. Thus, DSM-5 has divided bipolar disorder into two types. In *bipolar I disorder*, the person has had at least one manic episode and usually, but not necessarily, at least one major depressive episode as well. In *bipolar II disorder*, the person has had at least one major depressive episode and at least one hypomanic episode, but has never met the diagnostic criteria for manic episode. In a less common pattern, called the *rapid-cycling type*, the person (usually a woman) switches back and forth between depressive and manic or hypomanic episodes (with at least four mood episodes per year), with little or no "normal" functioning between (Leibenluft, 2000). This pattern, which tends to have a poor prognosis (Leibenluft, 2000), occurs naturally in some bipolar patients, but also occurs in about 25% of bipolar patients in response to antidepressant medication (Suppes, Dennehy, & Gibbons, 2000).

The occurrence of manic or hypomanic episodes is not all that differentiates bipolar disorder from major depression (Table 11.2; Rehm, Wagner, & Ivens-Tyndal, 2001). First, bipolar disorder is much less common than major depression, affecting an estimated 0.5–3.5% of the world population (Miklowitz & Johnson, 2006). Second, unlike major depression, bipolar disorder occurs in the two sexes with approximately equal frequency, and bipolar disorder is more prevalent among higher socioeconomic groups. Third, whereas people who are married or have intimate relationships are less prone to major depression, they are not at decreased risk for bipolar disorder. Fourth, people with major depression tend to have histories of low self-esteem, dependency, and obsessional thinking, whereas people with bipolar disorder are more likely to have a history of hyperactivity or ADHD (Sachs et al., 2000; Walshaw, Alloy & Sabb, 2010). Fifth, the depressive episodes in bipolar disorder are more likely to involve psychomotor retardation, excess sleep, weight/appetite increase than those in major depression (Benazzi, 2000, 2001). Sixth, bipolar disorder mood episodes are generally briefer and more frequent than are those in major depression (Cusin, Serretti, Lattuada, Mandelli, & Smeraldi, 2000). Seventh, bipolar disorder is associated

TABLE 11.2
Differences Between Bipolar Disorder and Major Depression

	Bipolar Disorder	Major Depression
Sex ratio	Equal	2 : 1 (women: men)
Course	More frequent, brief episodes	Less frequent, longer episodes
Prognosis	Greater impairment; but some outcomes of high accomplishment	Less impairment
Prevalence	0.5–4.4% of the US population	17% of the US population
Marital status	No difference in rates for married vs. unmarried people	Lower rates in married people
Depressive episodes	Psychomotor retardation common	Psychomotor retardation less common
Genetics	Strong heritability	Weaker heritability
Personality features	Hyperactivity, ADHD, impulsivity	Dependency, low self-esteem, and obsessional thinking

Source: Adapted from Alloy, Riskind, & Manos (2004). *Abnormal Psychology: Current Perspectives* (9th ed.)

with greater impairment in marital and work functioning, substance use, as well as heightened risk of suicide, and has a worse long-term outcome than major depression (Goodwin & Jamison, 2007; Judd et al., 2005; Kessler et al., 2006; Miklowitz & Johnson, 2006). Finally, bipolar disorder has a stronger genetic predisposition and therefore is more likely to run in families than major depression (Goodwin & Jamison, 2007). Although it was previously believed that major depression had an earlier age of onset than bipolar disorder, it is now common to see bipolar disorder diagnosed in children and adolescents as well, most likely because of greater awareness of the disorder in youth (Youngstrom, Birmaher, & Findling, 2008).

Depression and Bipolar Disorder Spectra Many people are chronically depressed or experience depressed and expansive mood periods that are not severe enough to merit a major depressive or manic episode diagnosis. Owing to the variation in mood disorders, from more mild and chronic to more severe and episodic, many researchers support the notion that both depression and bipolar disorder should be considered as continua or spectra as opposed to discrete disorders (Hankin, Fraley, Lahey, & Waldman, 2005; Merikangas et al., 2007).

Unipolar Depression Spectrum Depressions can manifest in many different ways and differ in severity and duration. DSM-5 recently changed the name of the prior diagnosis of dysthymic disorder to *persistent depressive disorder (dysthymia)*, which involves a mild, persistent depression that may occur for 2 or more years. Dysthymic individuals are typically morose, pessimistic, introverted, overconscientious, and incapable of fun (Akiskal & Cassano, 1997). In addition, these individuals often have lower energy, low self-esteem, and disturbances of eating, sleeping and thinking that are associated with MDD, but their functioning is worse (Klein, Schwartz, Rose, & Leader, 2000). Whereas dysthymia is chronic, MDD is usually episodic, although major depressive episodes can last months or longer. Dysthymia, like MDD, is 1.5–3 times more common in women than men and it has the same neurophysiological abnormalities and responses to antidepressant medication as MDD (Akiskal, Djenderedjian, Rosenthal, & Khani, 1997). In DSM-5, clinicians can make specifications of the severity of an episode of mild, moderate, or severe. Researchers have termed it *double depression* when an major depressive episode is superimposed on dysthymia. Double depression is considered to be on the more severe end of the unipolar depression spectrum. In essence, an individual with dysthymia may sink into a major depressive episode (about 77% of dysthymic individuals develop MDD; Klein et al., 2000) and then recover from the major depression but continue their mild, persistent dysthymia. Kessing (2007) examined the subtypes of depression in a large-scale epidemiological study and found no clear demarcation between mild, moderate, and severe depression, supporting a continuum. In addition, depressive symptoms may change over time; so that individuals change diagnosis from meeting criteria for MDD, to minor depression (a subthreshold episode), to dysthymia, and subsyndromal states (Kessing, 2007). Although all three disorders have high rates of recovery, people with double depression and dysthmia have more impaired social and physical functioning than those with MDD (Rhebergen et al., 2009). In addition, the more chronic dysthymia is characterized by a worse quality of life, inadequate social support, and slower rates of improvement compared to MDD (Klein, Shankman, & Rose, 2006; Subodh, Avasthi, & Chakrabarti, 2008). DSM-5 included a new diagnosis of *disruptive mood dysregulation disorder* to capture chronic and severe persistence of irritability that is often associated with emotional dysregulation and often leads to frequent temper outbursts.

Bipolar Spectrum Similar to the unipolar spectrum, bipolar disorder can manifest itself in many different ways. Like dysthymia, *cyclothymic disorder* is a chronic condition that may last for years and may never go a few months without a hypomanic or depressive phase. Cyclothymic disorder is mild and persistent and becomes a way of life. For instance, individuals with cyclothymic disorder come to depend on their hypomanic phase in order to work long hours and catch up on previously delayed tasks before slipping back into a normal or depressed state. Family members often describe cyclothymic individuals as "moody," "high-strung," "hyperactive," and "explosive" (Akiskal et al., 1977). Bipolar disorders appear to form a spectrum of severity from the milder, subsyndromal cyclothymic disorder, to bipolar II disorder, to full-blown bipolar I disorder at the most severe end (Cassano et al., 1999; Goodwin & Jamison, 2007). Three lines of evidence support this spectrum model. First, equivalent rates of bipolar disorder have been reported in the first- and second-degree relatives of cyclothymic disorder and bipolar I individuals (Akiskal et al., 1977; Depue et al., 1981), and increased rates of cyclothymic disorder are found in the first-degree relatives of bipolar patients (Chiaroni, Hantouche, Gouvernet, Azorin, & Akiskal, 2005). In addition, among monozygotic twins, when one twin had bipolar disorder, the co-twin had elevated rates of both bipolar and cyclothymic disorders (Edvardsen et al., 2008). These findings suggest that cyclothymic disorder shares a common genetic diathesis with bipolar disorder. Second, individuals with cyclothymic disorder, like bipolar I patients, often experience an induction of hypomanic episodes when treated with tricyclic antidepressants (Akiskal et al., 1977). Finally, individuals with cyclothymic disorder are at increased risk of developing bipolar I or II disorder when followed over time (Alloy, Urosevic et al., 2012; Birmaher et al., 2009; Kochman et al., 2005; Shen, Alloy, Abramson, & Grandin, 2008). Similar to unipolar depression, bipolar disorder also can carry a specifier of severity of mild, moderate, and severe.

Dimensions of Mood Disorder

In addition to the important distinctions between bipolar and depressive disorders, there are certain dimensions that researchers and clinicians have found useful in classifying mood disorders. We discuss three dimensions: psychotic versus non-psychotic, early versus late onset, and endogenous-reactive. In addition, we discuss the importance of life events in the onset of mood disorders, because this was the original basis of the endogenous-reactive distinction.

Psychotic Versus Non-psychotic Some individuals who have episodes of major depression or mania may also experience associated symptoms of psychosis. In fact, the diagnosis of MDD or bipolar disorder in DSM-5 can have the additional distinction of "with mood-congruent psychotic features" (American Psychiatric Association, 2013, pp. 152, 186). To get this qualifier for either a major depressive or a manic episode, the psychotic symptoms must occur during mood episodes. Whereas prior issues of the DSM differentiated psychotic mood disorders from the diagnosis of schizoaffective disorder by this mood qualifier, the DSM-5 can have a specifier of "with mood-incongruent psychotic features' that suggests the psychotic symptoms can be outside of a mood episode. Historically, the psychotic characterization was used to describe the severity of the episode, but more recent research suggests that there may be other factors at work (Forty et al., 2009; Bora, Yucel, Fornito, Berk, & Pantelis, 2008).

Major depressive disorder with psychotic features is not uncommon. Roughly 14% of individuals with MDD had a history of episodes with psychotic features (Johnson, Howarth, & Weissman, 1991). Crebbin, Mitford, Paxton and Turkington (2008) found that the diagnosis of psychotic depression was more prevalent than schizophrenia in first episodes of psychosis. In psychotic depression, hallucinations, delusions, and extreme withdrawal are usually congruent with the depressed mood. For instance, the content of these delusions or hallucinations is generally themed around personal inadequacy, guilt, or deserved punishment. Individuals with psychotic features have generally more severe depressive episodes and greater hormonal disturbances (Contreras et al., 2007). Importantly, the diagnosis of MDD with psychosis is relative unstable over time. Over 50% of individuals initially diagnosed with MDD with psychotic features switched diagnosis to bipolar disorder, schizophrenia, or schizoaffective disorder within 10 years (Ruggero et al., 2011).

Episodes of mania with psychotic features are more prevalent than depressive episodes with such features. Estimates of lifetime prevalence of psychotic features occurring during at least one manic episode range from 50–75% of those diagnosed with bipolar disorder (Ozyildrim, Cakir, & Yaziki, 2010; Canuso, Bossi, Zhu, Youssef, & Dunner, 2008). Although present to a lesser degree in many manic episodes, thoughts of grandiosity, lack of judgment/insight, and suspiciousness/persecution were at more delusional levels in those with psychotic features. One study found that working memory deficits may be a marker for differences between those with a diagnosis of bipolar disorder with psychosis and those without this specifier (Allen et al., 2010).

Researchers continue to debate whether mood disorders with psychotic features are distinct disorders or simply on the more severe end of a spectrum. Kraepelin (1921), in his original classification system, listed all incapacitating mood disorders under the heading "manic-depressive psychosis," which he considered distinct from those episodes at the non-psychotic-level. Some researchers still hold this position. For instance, Bora and colleagues (2008) suggest that a mood episode with psychotic features may be associated with different genetic and neurobiological markers compared with those without psychotic features. Other researchers argue that psychotic features are present only at the severe levels of a disorder. For instance, Ozyldirim and colleagues (2010) describe psychotic episodes of mania as more severe, more likely to lead to hospitalization, and less responsive to some medications.

Early Versus Late Onset Evidence over the last few decades suggests that age at onset is an important factor in the trajectory of mood disorders. In general, people who develop a mood disorder earlier have poorer outcomes. For example, individuals with recurrent MDD before 15 years of age had more clinical features, poorer social outcomes and psychosocial adjustment, and greater anxiety comorbidity than those without recurrent episodes (Hammen, Brennan, Keenan-Miller, & Herr, 2008). In addition, an earlier age of onset of depression is associated with a higher risk of suicide intent (Thompson, 2008) and with neural abnormalities in different brain regions (Chen et al., 2012). Further, those who developed an earlier onset of depression are more likely to misuse alcohol, harm themselves, and have higher rates of comorbidity (Voshaar, Kapur, Bickley, Williams, & Purandare, 2011). Heritability may play a role, as the earlier the onset of a depressive disorder, the more likely it is the person has relatives with a mood disorder (Klein et al., 1999).

In recent years, research also has shown similar trajectories in cases of early onset bipolar disorder. Oedegaard, Syrstad, Morken, Akiskal, & Fasmer (2009) found that about 60% of people with bipolar disorder had an early onset (before the age of 20 years) and 13% occurred in childhood (before 13 years of age). Childhood onset has been associated with a more chronic, severe, and recurrent course of disorder, with poorer functioning and quality of life than adult onset (Perlis et al., 2009; Birmaher et al., 2009). In addition, early onset was associated with a higher percentage of first-degree relatives with a history of mental illness (Baldessarini et al., 2012). Finally, research suggests a genetic difference for those who develop early onset bipolar disorder (Priebe et al., 2012).

Investigators have begun to examine the early onset of bipolar disorder in children and many researchers still

question the validity of this diagnosis. Bipolar disorder was recognized only recently in children and a lack of consensus on its features remains (Luby & Navsaria, 2010). Even though this issue remains controversial, the prevalence of new cases of bipolar disorder in children is increasing (Danner et al., 2009). Some suggest that the increased prevalence may be due to an increase in awareness of childhood onset (e.g., Moreno et al., 2007), whereas others argue that there is an increase in misdiagnosis (e.g., Danner et al., 2009).

Endogenous Versus Reactive Originally, the terms endogenous and reactive were used to identify whether or not a depressive episode was preceded by a precipitating event. Those linked to these stressful events were considered reactive, whereas those that were not linked to an event were called endogenous (literally, "born from within") and considered to have a more biological basis. Proponents of Kraepelin's tradition make a distinction between nonpsychotic depressions as generally reactive, whereas psychotic depressions are endogenous (Rehm et al., 2001).

Research has subsequently shown that most depressive episodes, including those in bipolar disorder, are preceded by stressful life events (Alloy, Abramson, Urozevic, Bender, & Wagner, 2009; Johnson & Kizer, 2002), and stressful events are a major cause of depressive episodes (Kendler, Karkowski & Prescott, 1999). In some cases, there is a precipitating event for the first episode, but life events become progressively less important for subsequent recurrences, an effect known as "kindling" (Morris, Ciesla, & Garber, 2010; Monroe & Harkness, 2005). Generally speaking, despite the definition of endogenous and reactive, these terms are no longer used to indicate whether there was a precipitating event, but to describe different patterns of symptoms (Rehm et al., 2001). Individuals who show marked anhedonia with associated physical symptoms, such as early morning awakening, weight loss, and psychomotor changes, are described as having a depression that is qualitatively different from those that occur after a death or loss of a loved one, and are thus characterized as endogenous. In DSM-5, this endogenous characteristic is referred to as melancholic features. Indeed, recent research confirms that those with melancholic features are more likely to report episodes coming "out of the blue" and to be more severe than those with depression without melancholic features (Parker, Fletcher, & Hadzi-Pavlovic, 2012).

The distinction between endogenous and reactive depression based on symptoms seems to have greater validity. Individuals with endogenous depression differ from those with reactive depression in their sleep patterns. Individuals who prefer evening activities have reported more severe depressive symptoms compared with others based on this biological characteristic (Hidalgo et al., 2009). People with endogenous depression also are more likely to show neurobiological abnormalities and respond to biological treatments, such as electroconvulsive therapy (Rush & Weissenburger, 1994). Accordingly, some researchers still suspect that endogenous depression is more biological, although there is some research to the contrary. For example, if endogenous depression were more biologically based, research would show that individuals with these features have greater family histories of depression, but numerous studies have shown that they do not (Rush & Weissenburger, 1994). In sum, the distinction between reactive and endogenous depression is generally based on symptom presentation, because most mood episodes, whether mania or depression, are preceded by life events.

Life Events in Depression and Bipolar Disorders Depression is usually precipitated by events that involve failures or uncontrollable interpersonal loss such as death, divorce, or separation (Cronkite & Moos, 1995, Kendler et al., 1999; Monroe Rohde, Seeley, & Lewinsohn, 1999). By the same token, if a person has social support in the form of close personal relationships, he or she is less likely to succumb to depression in the face of stressful life events (e.g., Panzarella, Alloy, & Whitehouse, 2006). Further, stressors that are in part dependent on the individual's behavior (such as a fight) are more likely to lead to depression than events that are independent of their behavior (such as a death in the family; Hammen, 2006; Liu & Alloy, 2010). In addition, some researchers postulate that if an individual holds a specific personality predisposition, events that are specifically congruent with that style predict mood symptoms (e.g., Francis-Raniere, Alloy, & Abramson, 2006). For instance, Francis-Raniere and colleagues (2006) showed that for personalities characterized by self-criticism and concern about performance evaluation, congruent negative and positive events predicted depressive and hypomanic symptoms, respectively.

The association between stressful life events and depressive or manic episodes differs for first onset of depression or mania and future recurrences. The kindling hypothesis, first postulated by Post (1992), suggests that stressful life events are important for the first onset, but that the association between events and episodes becomes weaker as the number of episodes increases (Bender & Alloy, 2011; Kendler, Thornton, & Gardner, 2000; Monroe & Harkness, 2005). Monroe and Harkness (2005) suggest two interpretations of these findings. The first interpretation is that subsequent episodes are less reliant on stressful events and eventually become autonomous; therefore, depressive episodes may occur without a precipitating event (Monroe & Harkness, 2005). Another interpretation is that an event may still be required to precipitate subsequent depressive episodes, but events can be of decreasing severity as individuals experience more episodes, wherein eventually minor events, daily hassles, or expectation of a stressful event could trigger an episode (Monroe & Harkness, 2005).

Similar to depressive disorders, stressful life events also have been shown to predict symptoms and episodes of mania and depression in bipolar disorder. In depression, negative life events generally precede an episode, whereas both negative and positive life events can precede a hypomanic/manic episode (Alloy, Abramson, Urosevic, Bender et al., 2009; Johnson, 2005). However, particular types of negative and positive events have been found to trigger bipolar mood episodes. For example, events that disrupt daily social routines (e.g., sleep/wake times, meal times), predict both depressive and hypomanic/manic symptoms and episodes (Malkoff-Schwartz et al., 1998, 2000; Sylvia et al., 2009). In addition, life events involving attainment of or striving toward a desired goal predict increases in manic symptoms or onsets of hypomanic episodes among individuals with bipolar spectrum disorders (Johnson et al., 2008; Nusslock et al., 2007). The psychological and neurobiological mechanisms by which life events trigger mood episodes are of considerable importance in ultimately understanding the causes of mood disorders.

Suicide

Suicide is defined as death from a self-inflicted injury committed with the intent to die. In addition to completed suicide, other suicidal behaviors include suicide attempts, which are defined as self-injurious behaviors committed with certain or ambivalent intent to die, and suicidal ideation, which consists of thoughts about being dead or killing oneself (Miller, Rathus, & Linehan, 2007). Of the many reasons why people take their own lives, depression and bipolar disorder are among the most common. MDD is the psychiatric diagnosis most commonly associated with suicide, with the risk of suicide among depressed individuals approximately 20 times greater than in the general population (Centers for Disease Control and Prevention, 2015). Individuals who have also had a manic episode are at even greater risk, with the rates of completed suicide among individuals with a bipolar disorder nearly 60 times greater than the general population (Fountoulakis, Gonda, Siamouli, & Rhimer, 2009).

Prevalence In 2011, the last year for which statistics are available, over 38,000 people died by suicide in the United States, making suicide the tenth leading cause of death. At this rate, approximately one suicide occurs every 14 minutes in the United States (Hoyert & Xu, 2012). These rates are even higher among younger populations, with suicide being the second leading cause of death for 15- to 24-year-olds and the fourth leading cause of death for 5- to 14-year-olds in the United States (Hoyert & Xu, 2012). These statistics do not account for those who engage in the wide range of suicidal behaviors, including thoughts, plans, gestures, and attempts, which are far more prevalent than completed suicide. Among adults in the United States between the years 2008 and 2009, approximately 8.3 million (3.7% of the adult U.S. population) reported having suicidal thoughts, 2.2 million (1.0% of the U.S. adult population) reported having suicidal plans, and 1 million (0.5% of the U.S. adult population) reported making a suicide attempt (Crosby, Han, Ortega, Parks, & Gfoerer, 2011).

Despite these high rates, suicide may still be underreported, for a variety of reasons. First, the deaths of many people who commit suicide may actually appear accidental. For example, the leading methods of suicide include firearms (50.5% of completed suicides), suffocation (24.7% of completed suicides), and poisoning (17.2% of suicides), and it is frequently difficult to determine whether death by these causes is accidental or purposeful (Earton, 2012). Furthermore, it has been estimated that approximately 15% of fatal automobile accidents are actually suicides (Finch, Smith, & Pokorney, 1970). Another obstacle to obtaining accurate statistics on the prevalence of suicide is the variability in the definition of suicide (Sainsbury & Jenkins, 1982). Although completed suicide is the most severe end of the suicidal spectrum, many other thoughts and behaviors may be considered suicidal. For example, individuals may experience suicidal thoughts, develop plans to commit suicide, or engage in non-fatal suicidal behaviors, such as cutting or burning themselves, without ever actually attempting or committing suicide. Because many behaviors characterize suicide, a consistent definition of suicide is needed to most effectively monitor the incidence of suicide and examine trends over time and across studies (Goldsmith, Pellmar, Kleinman, & Bunny, 2002).

Along these same lines, research suggests that an individual's intent to die must be taken into account when determining whether behaviors are suicide attempts or not (O'Carroll, Berman, Maris, & Moscicki, 1996). Research suggests that only 39% of people who attempt suicide are truly determined to die and that another 13% are ambivalent about dying (Kessler, Borges, & Walters, 1999). Furthermore, research within the first decade of the 21st century highlights the importance of differentiating suicidal behavior from non-suicidal self-injury, which is characterized by the direct destruction of bodily tissue without the intent to die (Nock, Joiner, Gordon, Lloyd-Richardson, & Prinstein, 2006). In sum, more accurate classification of suicidal behaviors is needed, as engagement in prior suicidal behavior, such as ideation and attempts, is among the best, if not the best, predictor of eventual completed suicide (e.g. Joiner et al., 2003; Kessler et al., 1999; Nock et al., 2008).

Risk Factors Given the costs of suicide to both society and individuals, a better understanding of the risk factors associated with suicide is critical (Hoyert & Xu, 2012). Risk factors may be stable or transitory, characteristic of the individual or of the environment, and they may have occurred in the past (distal) or be occurring in the present (proximal). Suicide is a complex phenomenon with many causes and is typically a culmination of a

variety of biological, psychiatric, and environmental factors (Rihmer, 2007; for a review of risk factors, see the U.S. Department of Health and Human Services' National Strategy for Suicide Prevention, 2001.)

Gender Although women are more likely than men to think about and attempt suicide, particularly during adolescence, males commit suicide at nearly four times the rate of females and represent approximately 79% of all completed suicides in the United States (Centers for Disease Control and Prevention, 2015; Lewinsohn, Rohde, Seeley, & Baldwin, 2001). A common explanation for this difference in completed suicide is that males tend to choose more lethal methods. Firearms are the most commonly used method of completed suicide among males, whereas poisoning is the most common method of completed suicide among females (Centers for Disease Control and Prevention, 2015).

Race/Ethnicity The highest rates of suicide are found among American Indian/Alaska Native adolescents and young adults (31 suicide deaths per 100,000) and among non-Hispanic White Americans (13.5 suicide deaths per 100,000). The lowest rates of suicide are seen among Hispanics (6 suicide deaths per 100,000) and non-Hispanic African Americans (5.1 suicide deaths per 100,000). These lower rates among African Americans and Hispanics, however, may be indicative of underreporting and misclassification rather than actual differences due to race/ethnicity (Centers for Disease Control and Prevention, 2015; Rockett, Samora, & Cohen, 2006).

Age In general, the risk of committing suicide increases as a function of age, particularly among males. Older adults are disproportionately likely to die by suicide, with 9 of every 100,000 females aged 45–54 years dying by suicide and 31 of every 100,000 males 75 and older dying by suicide (Centers for Disease Control and Prevention, 2015). Although rates are highest among older adults, suicide rates for adolescents and young adults between ages 15 and 24 have quadrupled among males and doubled among females over the past 60 years. Although suicide rates in this age group have declined almost 30% since 1994, suicide remains the second leading cause of death among 15- to 24-year olds (Hoyert & Xu, 2012). Approximately 16–17% of high-school students consider suicide, between 13% and 16.5% make plans for an attempt, and approximately 4–8% make an attempt each year (Grunbaum et al., 2002). Furthermore, for every completed youth suicide, it is estimated that 100–200 attempts are made (Centers for Disease Control and Prevention, 2015).

Sexual Orientation Research over the 1990 and 2000s suggests that lesbian, gay, and bisexual individuals are more likely than heterosexual individuals to attempt and commit suicide. This may be particularly true among youth (see Ploderl et al., 2013, for a review). Researchers hypothesize that increased social stressors among these populations, including peer victimization, "anti-gay" social climates, and physical abuse by parents contribute to increased rates of depression and substance use, thus conferring additional risk for suicide (Hatzenbuehler, 2011).

Biology/Genetics Twin and adoption studies show that the predisposition to engage in suicidal behavior may be at least partly inherited. Relatives of individuals who have died by suicide are two to six times as likely to commit suicide themselves (Mann et al., 2009), and children of parents who suffer from mental health disorders are more likely to engage in suicidal behavior (Gureje et al., 2011). Although the specific genes responsible for increased suicide risk are unknown, genes related to the neurotransmitter serotonin may be potential candidates for suicidal behavior, as altered brain serotonin functioning has been associated with attempted and completed suicide among individuals with depression (Galfalvy, Huang, Oquendo, Currier, & Mann, 2009). In addition, hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis has been implicated as a risk factor for suicide in major depression (Coryell, Young, & Carroll, 2006).

Mental Disorders Attempted and completed suicides are very rare in the absence of a major mental disorder (Beautrais, Joyce, Mulder, & Fergusson, 1996), and psychiatric risk factors are often the most powerful and clinically useful predictors of suicide. Approximately 90% of people who attempt or commit suicide have at least one (usually untreated) major mental disorder. The most common disorders associated with suicide are major depression (56–87% of suicide attempts and completions), substance use disorders (26–55%), and schizophrenia (6–13%). In addition, individuals with depression or bipolar disorder who commit or attempt suicide most often do so during a major depressive episode and very rarely during mania (Rihmer, 2007). Specific risk factors within major depressive episodes, in order of significance, include: (1) current suicidal ideation, plan, or wish to die; (2) prior suicide attempt; (3) severe depression characterized by hopelessness and/or guilt; (4) current or recently released psychiatric inpatient status; (5) diagnosis of bipolar II, followed by bipolar I, followed by unipolar depression; 6) depressive mixed states; (7) cyclothymia; (8) psychotic symptoms; and (9) concurrent anxiety disorders, substance use, and serious medical illness (Coryell & Young, 2005; Fiedorowicz et al., 2009; Rihmer, 2007; Oquendo et al., 2004).

Protective Factors Certain factors may actually decrease the risk for suicide. These protective factors include effective treatment for mental disorders and substance abuse, easy access to treatment and support for help seeking,

family and adult/teacher/community support, cultural and religious beliefs that discourage suicide, and skills in problem solving and active coping (Centers for Disease Control and Prevention, 2015; Eisenberg, Ackard, & Resnick, 2007; Meadows, Kaslow, Thompson, & Jurkovic, 2005).

Predicting and Preventing Suicide The friends and family members of individuals who commit suicide are often shocked, indicating that they saw no signs that their loved one was at risk. Despite this fact, most suicidal people clearly communicate their intent prior to their death, often to their close relatives. Also, most individuals who commit suicide have visited a psychiatrist or general practitioner within weeks or months of their fatal attempt (Isometsä, Henriksson, Aro, & Heikkinen, 1994). Research suggests, however, that upon these visits to professionals, suicidal individuals were either prescribed vitamins or improper psychotropic medications (Rutz, 1996). Clearly, the recognition and management of pre-suicidal individuals are poor (Oquendo, Malone, Ellis, Sackeim, & Mann, 1999). Solutions to this problem include better recognition of the signs of suicide, greater awareness of treatment possibilities, and improved training for non-psychiatric health care professionals and other key personnel who are in positions to recognize the signs of suicide (Gonda, Fountoulakis, Kaprinis, & Rihmer, 2007).

If suicide can be predicted, then perhaps it can be prevented. Researchers have identified several key areas of suicide prevention, including 1) providing education and awareness about the signs of and effective treatments for suicide directed both to the general public and to healthcare providers and school personnel; 2) implementing screening tools for identifying individuals most at risk of suicide so that these individuals might be directed to appropriate treatment; 3) increasing access to mental health services and effective treatments for psychiatric disorders, as individuals who receive appropriate treatment for an underlying psychiatric disorder have the highest likelihood of recovery (Rudd & Joiner, 1998); 4) implementing effective suicide prevention programs; 5) restricting access to lethal means such as firearms, as this may delay a suicide attempt and allow time for the individual to seek help; and 6) managing how suicide is portrayed and reported in the media, as research supports a connection between media portrayals and subsequent increases in suicide rates, particularly among youth (Gould, Jamieson, & Romer, 2003). For reviews, see Mann et al., (2005) and U.S. Department of Health and Human Services (2001).

Mood Disorders: Causes and Treatments

Most theories of the causes of mood disorders, as well as treatments for mood disorders, have focused on depression because it is far more common than hypomania and mania. However, some theoretical perspectives have addressed bipolar disorder as well, and we discuss some of these. Among the general theoretical approaches to mood disorders, behavioral/interpersonal, cognitive, and neuroscience perspectives have had the greatest influence on understanding the causes of and generating treatments for mood disorders. Thus, we present these three perspectives in greater detail and then discuss the psychodynamic approach more briefly.

Interpersonal Perspective Interpersonal theories of depression (e.g., Coyne, 1976; Joiner, 2000; Giesler, Josephs, & Swann, 1996) focus on the social context of depression. According to interpersonal formulations, depressed individuals engage in various maladaptive interpersonal strategies in an attempt to improve or regulate mood. But, these strategies are typically unsuccessful.

Excessive Reassurance Seeking Excessive reassurance seeking is an aversive behavioral style in which depressed individuals persistently seek reassurance that others care about and value them (Coyne, 1976). Coyne posits that whereas the act of reassurance seeking is an individual's behavioral attempt at changing or improving their depressed state, the behavior actually serves to maintain the depression and worsens the individual's interpersonal environment. The excessive reassurance seeking irritates and drives away friends and family members, leaving the individual rejected (Joiner, Metalsky, Katz, & Beach, 1999) and with a weakened social support network (Potthoff, Holahan, & Joiner, 1995). The depressed individual uses this withdrawal as evidence for depressive cognitions (e.g., "I'm unlovable"). The generated stress and further entrenchment of these depressive beliefs serves to deepen the depression in a self-perpetuating cycle (Joiner, 2000). A meta-analytic review of 38 (N = 6,973) cross-sectional studies examining the relationship between depression and excessive reassurance seeking (Starr & Davila, 2008) revealed a moderate effect size (r = .32) between excessive reassurance seeking and depression. Indeed, excessive reassurance seeking has been found to predict subsequent increases in depressive symptoms in both adults and youth (e.g., Abela, 2005; Davilla, 2001; Joiner, Metalsky, Gencoz & Gencoz, 2001; Joiner et al., 1999).

Negative Feedback Seeking Giesler, and colleagues (1996) suggest that depressed individuals actually seek out rejection and negative feedback from others. They propose that depressed individuals find rejection and negative feedback more predictable and in line with their negative self views. However, the presence of these negative stressors may serve to deepen the depression rather than relieve it. Researchers have found support for the transactional relationship between negative feedback, rejection, and depression (Borelli & Prinstein, 2006; Pettit & Joiner, 2001; Joiner et al., 1999).

Behavioral Perspective

Extinction Early behavioral theories focused on the relationship between external reinforcers and behavior. Many

behaviorists regard depression as a result of behavioral extinction (Fester, 1973; Lewinsohn, 1974; Jacobson, Martell, & Dimidjian, 2001). Generally, the behavioral theory of depression suggests that once behaviors are no longer rewarded (reinforced), individuals cease to perform these behaviors that were previously rewarded (extinction). Through the resulting withdrawal and inactivity, individuals become depressed. The behavioral theorists propose several reasons for the reduction in positive reinforcement that leads to the extinction of behaviors and subsequent depression. For example, Lewinsohn (1974) proposed that positive reinforcement is influenced by the number of available reinforcers in the environment, the range of stimuli that the individual finds reinforcing, and the ability of the individual to obtain reinforcement from the environment. In addition, Ferster (1973) proposed that changes in the environment and the increased passivity of the individual could influence the frequency of reinforcement of behaviors.

A number of studies have supported the extinction perspective on depression. Lewinsohn and colleagues conducted several studies supporting a direct correlation between the number of pleasurable activities engaged in and depression (e.g. Lewinsohn & Graf, 1973; MacPhillamy & Lewinsohn, 1974). In fact, one of the most prominent objections to this model of depression has been that depressed individuals may lack the ability to have a pleasurable response to positively reinforcing stimuli (anhedonia), rather than just lacking positively reinforcing stimuli themselves.

Behavioral Activation Therapy In keeping with the extinction theory, behavioral activation treatment for depression is designed to increase activity and, in turn, develop more positively reinforcing behavior patterns in depressed individuals (Lewinsohn, Biglan, & Zeiss, 1976; Martell, Addis, & Jacobson, 2001). Jacobson and colleagues (2001) found that even severely depressed people show an elevation in mood if they are more behaviorally active and, thus, experience increased positive reinforcement. The authors describe that in behavioral activation, therapists help clients engage in planned activities, creating positive reinforcement and alleviating depressed mood. In behavioral activation, the client and therapist identify specific activities (positively reinforcing behaviors) that the client deems to be most helpful. Clients are then encouraged to engage in the activity based on a predetermined schedule, whether they feel like it or not in the moment. Depending on the success of the behavior in alleviating mood or improving quality of life, clients are asked to continue engaging in the behavior. Over time, clients are asked to engage in progressively more difficult activities, from getting out of bed at a regularly scheduled time to engaging in positive interpersonal activities. These changes break and reverse the cycle of sad mood, decreased activity, and withdrawal. More recent variants of behavioral activation include a values component early in therapy to identify pleasurable activities that may be more consistent with the client's core values (e.g., Lejuez, Hopko, & Hopko, 2003).

Substantial research lends support for behavioral activation as a successful treatment for depression. Behavioral activation therapy has been found to both reduce acute depression and prevent relapse over a 2-year follow-up (Jacobson et al., 1996; Gortner, Gollan, Dobson, & Jacobson, 1998). Several recent meta-analyses supported the utility of behavioral activation in treating depression (Cuijpers, van Straten, & Warmerdam, 2007; Ekers, Richards & Gilbody, 2008; Mazzucchelli, Kane, Rees, 2009). In general, the reviews found that activity scheduling/behavioral activation treatments for depression were as effective as other interventions (e.g. cognitive therapy) and more effective than control conditions in alleviating depression. For example, Cuijpers and colleagues' (2007) review of 16 randomized trials (N = 780 clients) of behavioral activation found a large pooled effect size of 0.87 (95% confidence interval: 0.60–1.15) with similar levels of depressive symptom reduction in individuals receiving behavioral activation as in those receiving comparable treatments (e.g., cognitive therapy). Their analysis also found that overall behavioral activation gains were maintained over time.

A review of the literature assessed the different specific treatment components of behavioral activation and their effectiveness (Kanter et al., 2010). The identified components include activity monitoring, assessment of life goals and values, activity scheduling, skills training, relaxation training, contingency management, procedures targeting verbal behavior, and procedures targeting avoidance. The authors found that activity scheduling, relaxation, and skills training interventions received empirical support on their own. All other techniques were effective, but only within larger treatment packages. Thus, they found that the most important components of behavioral activation were activity monitoring and scheduling in line with the main extinction theory of depression.

Behavioral treatments for depression also have included social skills training, aimed at ameliorating the aversive interpersonal behavior such as reassurance seeking and negative feedback seeking. Social skills training teaches depressed clients basic techniques to engage in satisfying social interactions through modeling of positive interpersonal behaviors by the therapist and role-playing by the client. Many behavioral treatments for depression are multifaceted, involving both behavioral activation and social skills training.

Cognitive Perspective Depression and mania involve changes in emotional, motivational, cognitive, and physical functioning. Cognitive theories of mood disorders hold that the cognitive changes are the crucial factor. According to cognitive formulations, the way people think about themselves, the world, and the future gives rise to the other phenomena in depression and mania.

Helplessness and Hopelessness The hopelessness theory of depression (Abramson, Metalsky, & Alloy, 1989) was derived from earlier work on learned helplessness (Seligman, 1975). Learned helplessness was first demonstrated with laboratory dogs. Seligman and his colleagues found that when dogs were exposed to inescapable electric shocks and then later were subjected to escapable shocks, they either did not try to escape or were slow and inept at escaping. The investigators concluded that when the shocks were inescapable, the dogs had learned that they were *uncontrollable*—a lesson they continued to act upon later even when it was possible to escape the shocks (Maier, Seligman & Solomon, 1969; Peterson, Maier, & Seligman, 1993). Seligman (1975) noted that this phenomenon closely resembles depression—that depression is a reaction to seemingly inescapable stressors in which the person learns that he or she lacks control over reinforcement and as a result gives up. The learned helplessness model is consistent with the finding that uncontrollable loss events typically precipitate depressive episodes. Note the difference between the learned helplessness and extinction theories. The crucial factor in extinction theory is an objective environmental condition—the lack of positive reinforcement—whereas the crucial factor in learned helplessness is a subjective cognitive process, the *expectation* of lack of control over reinforcement.

Exposure to uncontrollable (versus controllable) stress results in neurobiological changes consistent with depression (Minor & Saade, 1997; Maier & Watkins, 2005), and depressed patients who see themselves as helpless tend to show higher levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), a product of norepinephrine metabolism (Samson, Mirin, Hauser, Fenton, & Schildkraut, 1992). Norepinephrine abnormalities are often found in depressed people. In addition, positron emission scans of people doing unsolvable problems, which tend to produce learned helplessness, show that learned helplessness is associated with increased limbic system brain activity. The limbic system is also implicated in the processing of negative emotions such as depression (Schneider et al., 1996).

The original learned helplessness model had certain weaknesses. Although it explained the passivity characteristic of depression, it did not explain the equally characteristic sadness, guilt, and suicidal thoughts, or that different cases of depression vary considerably in severity and duration. Consequently, Abramson and colleagues (1989) revised the helplessness model to a hopelessness theory. According to the hopelessness theory, depression depends not just on the belief that there is a lack of control over reinforcement (a *helplessness expectancy*), but also on the belief that negative events will persist or recur (a *negative outcome expectancy*). When a person holds both of these expectations—that bad things will happen and that there is nothing one can do about it—he or she develops hopelessness, and it is this hopelessness that is the immediate cause of the depression (Abramson et al., 1989).

Hopelessness, in turn, stems from the inferences people make regarding stressful life events, that is, the perceived causes and consequences of such events. People who see negative life events as due to causes that are (1) stable (permanent rather than temporary); (2) global (generalized over many areas of their life rather than specific to one area of their functioning); and (3) internal (part of their personalities, rather than external, or part of the environment) are at greatest risk for developing hopelessness and, in turn, severe and persistent depression. Similarly, people who infer that stressful events will have negative consequences for themselves or who infer that the occurrence of stressful events means that they are incompetent and unworthy are more likely to become hopeless and depressed. In fact, Abramson et al. (1989) proposed that *hopelessness depression* constitutes a distinct subtype of depression, with its own set of causes (negative inferential styles combined with stress), symptoms (passivity, sadness, suicidal tendencies, low self-esteem), and appropriate treatments. This theory also applies to suicide. Hopelessness is the best single predictor of suicide, even better than depression (Beck, Brown, Berchick, Stewart, & Steer, 2006; Abramson et al., 2000).

The hopelessness theory has been extensively tested with mostly positive results. Depressed individuals are more likely than non-depressed individuals to attribute negative events to internal, stable, and global attributions (Joiner & Wagner, 1995; Sweeney, Anderson, & Bailey, 1986) and to exhibit expectations of low control or helplessness (Weisz, Southham-Gerow, & McCarty, 2001). Moreover, a negative inferential style is relatively stable over many years (Romens, Abramson, & Alloy, 2009) and predicts who has been depressed in the past (Alloy, Abramson, Hogan et al., 2000), who among never depressed individuals will develop a first onset of major depression and hopelessness depression (Alloy, Abramson, Whitehouse et al., 2006), who will become suicidal in the future (Abramson, Alloy, Hogan et al., 1998), and who, having recovered from depression, will relapse or have a recurrence (Illardi, Craighead, & Evans, 1997; Alloy, Abramson, Whitehouse et al., 2006). It also predicts who will have a worse course of depression (Iacoviello, Alloy, Abramson et al., 2006) and who, in a group of depressed people, will recover when exposed to positive events (Needles & Abramson, 2003).

Moreover, consistent with the vulnerability stress hypothesis of the hopelessness theory, many studies have found that the combination of a negative inferential style (the vulnerability) and exposure to negative life events (the stress) predicts subsequent increases in depressive symptoms (e.g., Abela, Stolow, Mineka, Yao, & Zhu, 2011; Gibb, Beevers, Andover & Holleran, 2006; Hankin, Abramson, Miller, & Haeffel, 2004). Other studies have shown that the reason a combination of stress and negative inferential style predicts depression is that this combination predicts hopelessness. It is hopelessness that, in turn, predicts depression (Alloy & Clements, 1998; Iacoviello, Alloy, Abramson, & Choi, 2010; Hamilton, Shapero et al.,

2013). Finally, people who show this combination also exhibit many of the symptoms hypothesized to be part of the hopelessness depression subtype (Alloy, Just, & Panzarella, 1997; Alloy & Clements, 1998; Iacoviello et al., 2013), and these symptoms cluster to form a distinct dimension of depression (Joiner, Steer et al., 2001). However, there is also conflicting evidence. For example, some researchers have found that the negative attributional style and stress combination does not necessarily lead to depression (Cole & Turner, 1993; Lewinsohn, Joiner, & Rohde, 2001).

Given that much evidence indicates that a negative inferential style does make people vulnerable to depression, it is important to discover the developmental origins of this cognitive vulnerability. Both social learning factors and a history of maltreatment may contribute to the development of negative inferential styles and depression. Individuals whose parents had negative cognitive styles, provided negative inferential feedback about the causes and consequences of stressful events in the individual's life (e.g., told their child, "You weren't invited to that party because you're unpopular, and now you'll be seen as a social outcast at school"), and whose parenting was low in warmth and affection are more likely to have negative cognitive styles as adults (Alloy, Abramson, Tashman et al., 2001; Garber & Flynn, 2001; Ingram & Ritter, 2000). In addition, people with childhood histories of emotional abuse from either parents or nonrelatives (peers, teachers, etc.) are also more likely to have negative cognitive styles as adolescents or adults (Gibb, Abramson, & Alloy, 2004; Gibb et al., 2001; Hamilton, Shapero et al., 2013). Emotional maltreatment also predicts onsets of depressive episodes (Liu et al., 2009). Thus, a history of negative emotional feedback and abuse may lead to the development of later cognitive vulnerability to depression. However, prospective studies beginning in childhood are needed to test this hypothesis.

Negative Self-Schema A second major cognitive theory of depression, Beck's (1967, 1987) negative self-schema model, evolved from his findings that the thoughts and dreams of depressed patients often contain themes of self-punishment, loss, and deprivation. Self-schemata are memory representations about the self that guide the way individuals process information from the environment such that individuals' attention is directed toward information that is congruent with the content of their self-schemata. Beck hypothesized that individuals who have negative self-schemata involving themes of inadequacy, failure, loss, and worthlessness are vulnerable to depression. Such negative self-schemata are often represented as a set of dysfunctional attitudes, such as "I am nothing if I do not succeed at this job," in which the person believes that his or her self-worth is dependent on being perfect or on others' approval. Further, when confronted with a negative life event, individuals with this type of cognitive style are hypothesized to develop negatively biased perceptions of themselves (low self-esteem), their personal world, and their future (hopelessness). According to Beck, this negative bias—the tendency to see oneself as a "loser"—is the fundamental cause of depression. If childhood experiences lead someone to develop a cognitive schema in which the self, the world, and the future are viewed in a negative light, that person is then predisposed to depression. Stress can easily activate the negative schema, and the consequent negative perceptions merely strengthen the schema (Beck, 1987; Clark, Beck, & Alford, 1999).

Research supports Beck's claim that depressed individuals have unusually negative self-schemata (Dozois & Dobson, 2001; Mathews & MacLeod, 2005) and that these schemata can be activated by negative cues. Negative self-schemata can also be activated by sad mood in people who have recovered from depression (Ingram, Miranda, & Siegel, 1998; Gemar, Segal, Sagrati, & Kennedy, 2001), and such reactivated negative schemata predict later relapse and recurrence of depression (Segal, Gemar, & Williams, 1999). There is also strong evidence that depressed individuals recall negative material more easily than positive material (Mathews & MacLeod, 2005) and recall autobiographical memories that are overly general rather than specific (Williams et al., 2007). The evidence that depressed individuals exhibit attentional biases toward negative stimuli is much more mixed; however, other findings provide stronger support for the notion that depressed individuals have difficulty inhibiting or disengaging their attention from negative material once they attend to it (Gotlib & Joorman, 2010; Koster, Lissnyder, Derakshan & De Raedt, 2011). This difficulty may underlie depressed individuals' tendency to persistently ruminate on their negative affect and the causes and consequences of their negative mood (Gotlib & Joorman, 2010; Koster et al., 2011). Rumination, in turn, has been found to predict subsequent onset of major depressive episodes (Nolen-Hoeksema, 2000; Spasojevic & Alloy, 2001; Robinson & Alloy, 2003) and more severe depressions (Nolen-Hoeksema, Wisco & Lyubomirsky, 2008).

Other studies indicate that people at high risk of depression, based on having negative cognitive styles, a past history of major depression, or parents who are depressed, selectively attend to and remember more negative than positive information about themselves (Alloy, Abramson, Murray et al., 1997; Ingram & Ritter, 2000; Taylor & Ingram, 1999). Still other research suggests that depressed individuals may have two distinct types of negative self-schemata, one centered on dependency, the other on self-criticism (Nietzel & Harris, 1990). For those with dependency self-schemata, stressful interpersonal events involving rejection or abandonment lead to depression. For those with self-criticism schemata, achievement failures should trigger depression. This hypothesis has been supported more strongly for dependency self-schemata and social events than for self-criticism schemata and failure (Coyne & Whiffen, 1995).

Although Beck's negative self-schema model of depression hypothesizes that depressed people exhibit

systematic biases in their processing of negative information, some evidence suggests that depressed individuals' pessimism is sometimes realistic, a phenomenon known as "depressive realism" or the "sadder but wiser" effect (Alloy & Abramson, 1988; Alloy, Wagner et al., 2010). For example, Lewinsohn, Mischel, Chaplin and Barton (1980) found that depressed individuals' evaluations of the impression they had made on others were more accurate than those of two non-depressed groups, both of whom thought they had made more positive impressions than they actually had. Similarly, Alloy and Abramson (1979) found that depressed people were far more accurate in judging how much control they had over outcomes than were non-depressed participants, who tended to overestimate their control when they were doing well and to underestimate it when they were doing poorly. Thus, it may be that non-depressed people are optimistically biased and that such biases are essential for psychological health (Alloy & Abramson, 1988; Haaga & Beck, 1995; Alloy, Wagner et al., 2010). Research supports this view. Alloy and Clements (1992), for example, found that individuals who were inaccurately optimistic about their personal control at baseline were less likely than more realistic participants to become depressed a month later in the face of stress.

Although most research on the cognitive theories of depression (both Beck's theory and the hopelessness theory) has focused on unipolar depression, findings suggest that cognitive models may be applicable to bipolar disorder as well. Individuals with bipolar disorders exhibit cognitive styles and self-schemata that are as negative as those with unipolar depression (Alloy, Abramson, Walshaw, Keyser et al., 2006; Alloy, Abramson, Walshaw, & Neeren, 2006). Moreover, negative cognitive styles combine with life events to predict subsequent increases in hypomanic/manic and depressive symptoms among people with bipolar disorder (Francis-Raniere et al., 2006; Reilly-Harrington, Alloy, Fresco, & Whitehouse, 1999). However, evidence suggests that the cognitive styles of individuals with bipolar spectrum disorders have a distinct character; they are specific to themes of high incentive motivation, goal striving, and reward sensitivity (Alloy, Abramson, Walshaw, Gerstein et al., 2009; Lam, Wright, & Smith, 2004).

Behavioral Approach System Dysregulation The distinctive nature of cognitive styles among bipolar individuals is consistent with the behavioral approach system (BAS) hypersensitivity model of bipolar spectrum disorders. The BAS hypersensitivity model is a motivational cognitive theory of bipolar disorder, originally developed by Depue and Iacono (1989) and expanded by Alloy and Abramson (2010), Alloy, Abramson, Urošević, Bender et al. (2009) and Urošević, Abramson, Harmon-Jones, and Alloy (2008). The BAS regulates approach motivation and goal-directed behavior. It is activated by rewards or external or internal goal-relevant cues. BAS activation is implicated in the generation of positive goal-striving emotions such as happiness (Gray, 1994). In addition, the BAS has been linked to a reward-sensitive neural network involving dopamine neurons that project between several emotion- and reward-relevant limbic and cortical brain systems (Depue & Iacono, 1989). According to the BAS hypersensitivity model, an overly sensitive BAS that is hyperreactive to relevant cues increases a person's vulnerability to bipolar disorder. When vulnerable individuals experience events involving rewards or goal striving and attainment, their hypersensitive BAS becomes excessively activated, leading to hypomanic/manic symptoms, such as increased energy, optimism, euphoria, decreased need for sleep, grandiosity, and excessive goal-directed behavior (see also, Johnson, 2005; Johnson, Edge, Holmes, & Carver, 2012). Alternatively, in response to events involving irreconcilable failures, losses, or non-attainment of goals, their overly sensitive BAS becomes excessively deactivated, leading to a shutdown of behavioral approach and depressive symptoms, such as decreased energy, sadness, loss of interest, hopelessness, and decreased motivation and goal-directed activity.

Recent evidence supports the BAS hypersensitivity model. Individuals with bipolar spectrum disorders exhibit significantly higher levels of self-reported BAS sensitivity and reward responsiveness on behavioral tasks than do individuals without mood disorders (see Alloy & Abramson, 2010; Urošević et al., 2008 for reviews). As noted above, they also exhibit BAS-relevant cognitive styles (Alloy, Abramson, Walshaw, Gerstein et al., 2009) and overly ambitious goal striving and goal setting, as well as greater cognitive reactivity and positive generalization in response to success experiences (Johnson et al., 2012). Furthermore, they typically exhibit increased relative left frontal cortical activity on electroencephalography, a neurobiological indicator of BAS sensitivity and activation, both at rest and in response to rewards (Coan & Allen, 2004; Harmon-Jones et al., 2008). Moreover, high BAS sensitivity predicts first onset of bipolar spectrum disorders in individuals with no prior history of bipolar disorder (Alloy, Bender et al., 2012), faster time to onset of hypomanic and manic episodes (Alloy, Abramson, Walshaw, Cogswell et al., 2008), and a greater likelihood of progressing to a more severe bipolar diagnosis over follow-up among bipolar spectrum individuals (Alloy, Urošević et al., 2012). Finally, as noted previously, life events involving goal striving or attainment are especially likely to trigger hypomanic or manic episodes among bipolar spectrum individuals (Johnson et al., 2008; Nusslock et al., 2007), consistent with the BAS hypersensitivity model.

Cognitive Behavioral Therapy Beck and his colleagues developed a multifaceted therapy that includes behavioral assignments, modification of dysfunctional thinking, and attempts to change schemata (Beck, Rush, Shaw, & Emery, 1979). Cognitive behavioral therapy (CBT) identifies, challenges, and ultimately aims to modify cognitive

schemata to generate less negative information processing (Hollon, 2006). The alteration of schemata is considered most important and, according to Beck's theory, will immunize the patient against future depressions. First, however, the therapist attempts to remediate the current depression, through "behavioral activation"—that is, getting the patients to engage in pleasurable activities (see the discussion of behavioral activation therapy above)—and by teaching them ways of testing and challenging their dysfunctional thoughts. Depressed patients are asked to record their negative thoughts, together with the events that preceded them. They are then asked to counter such thoughts with rational responses and record the outcome. In addition, with the therapist's help, depressed patients are encouraged to conduct behavioral "experiments" that also allow them to test and challenge the veracity of their dysfunctional thoughts. CBT also includes *reattribution training*, which aims to correct negative attributional styles (Beck et al., 1979). Patients are taught to explain stressful events in more constructive ways ("It wasn't my fault—it was the circumstances," "It's not my whole personality that's wrong—it's just my way of reacting to strangers") and to seek out information consistent with these more hopeful attributions. A similar approach is used with suicidal patients. Beck and colleagues see this as a way of correcting negative bias and combating hopelessness.

In some encouraging evaluations, CBT has been shown to be at least as effective as medication (e.g., DeRubeis et al., 2005; DeRubeis, Siegle, & Hollon, 2008). A combination of CBT and pharmacotherapy may have a slight advantage when compared with either treatment by itself (DeRubeis et al., 2008; Kupfer & Frank, 2001). Moreover, some studies have supported less relapse and recurrence for CBT than for pharmacotherapy (e.g., Dobson et al., 2008; Hollon et al., 2005; Jarrett et al., 2001). There is also some debate as to whether CBT works as well as medication for severely depressed patients (DeRubeis, Gelfand, Tang, & Simons, 1999; Blackburn & Moorhead, 2000), but other studies suggest that it does (e.g., DeRubeis et al., 2005; Fournier et al., 2009).

Furthermore, there is controversy about the mechanisms by which CBT produces change. For example, there is evidence that CBT produces changes both in negative cognitions, as it is hypothesized to work, as well as in abnormal neurobiological processes (Blackburn & Moorhead, 2000; DeRubeis et al., 2008). So whether it works through the proposed cognitive mechanism or by changing biological processes in unclear. However, some studies indicate that much of the depression symptom improvement in CBT occurs in one between-session interval, called "sudden gains," and that these sudden gains appear to be associated with the correction of patients' negative beliefs in the immediately preceding therapy session, consistent with a cognitive mechanism of treatment efficacy (Tang et al., 2005, 2007). Also, as noted, Beck's CBT is multifaceted, including behavioral activation, together with cognitive restructuring. Some studies found that the behavioral activation component of CBT worked as well as the entire treatment package, both at alleviating depression and at preventing relapse (Dobson et al., 2008; Gortner, Gollan, Dobson, & Jacobson, 1998). Thus, it could be that CBT is just as effective without its cognitive components. Regardless of how it works, CBT does indeed work. Thus, recent efforts have extended this approach successfully to the prevention of depression in children and adolescents (e.g., Brunwasser, Gillham, & Kim, 2009; Garber et al., 2009). For example, the Penn Resiliency Program (Brunwasser et al., 2009) is a group intervention designed for late elementary and middle-school students that teaches cognitive behavioral and social problem-solving skills and is based on the Beck and hopelessness theories of depression. The Penn Resiliency Program has demonstrated some success in preventing symptoms of anxiety and depression among youth and its effects can be long-lasting (Gillham, Hamilton, Freres, Patton, & Gallop, 2006). CBT also has been extended to the treatment of patients with bipolar disorder as an adjunct to mood-stabilizing medications (Basco, 2000; Newman, Leahy, Beck, Reilly-Harrington, & Gyulai, 2002), with some success (see Nusslock, Abramson, Harmon-Jones, Alloy, & Coan, 2009, for review). Nusslock and colleagues (2009) suggested that considering the implications of BAS hypersensitivity in bipolar disorder might further improve the effectiveness of CBT for bipolar conditions.

CBT has also been modified further to incorporate mindfulness techniques. Mindfulness was adopted from eastern traditions such as Buddhism and refers to a mental state during which the individual aims to harness his or her attention and focus on momentary somatic, sensory, environmental, and cognitive experience in an open and accepting manner (Bishop et al., 2004; Kabat-Zinn, 1994; Marlatt & Kristeller, 1999). Mindfulness involves the self-regulation of attention and the development of an open/accepting orientation to the present moment upon which that attention is focused. In mindfulness practice, meditation exercises are used to help individuals develop this skill to focus on bodily, cognitive, and emotional experiences. Segal, Williams and Teasdale (2002) developed mindfulness-based cognitive therapy to help depressed individuals develop a decentered view of their thoughts, emotions, and sensations. They suggest that viewing these occurrences as mental events rather than reflections of reality changes the way one relates to thoughts, thereby breaking down the process through which maladaptive thoughts and mental processes (rumination) maintain depression. Recent reviews suggest that mindfulness-based CBT is effective in treating depression and reducing relapse rates (Coelho, Canter, & Ernst, 2007; Hofmann, Sawyer, Witt, & Oh, 2010) and as effective as pharmacotherapies in preventing relapse (Kuyken et al., 2008; Segal, 2010).

Acceptance and Commitment Therapy Acceptance and commitment therapy (ACT; Hayes, Strosahl, & Wilson, 1999) is often referred to as a 'third wave' of CBT. ACT,

like CBT, combines cognitive and behavioral components, but is based on relational frame theory (Hayes, Barnes-Holmes, & Roche, 2001), a contextual theory of language and cognition. ACT consists of six core components including acceptance, defusion, contact with the present moment, self as context, values, and committed action. Unlike CBT, the primary aim of ACT is not symptom reduction but rather increased psychological flexibility, or the ability to contact one's present moment experiences more fully and to engage in values-consistent behavior. Thus, the treatment aims to help individuals increase their acceptance of their subjective experiences. These experiences include distressing thoughts, beliefs, sensations and feelings. Orienting behaviors toward living life in line with one's values (e.g., moving toward desired relationships or career goals) is thought to improve the individual's quality of life. A central feature of ACT is learning to view attempts to control unwanted experiences such as negative emotions or thoughts as ineffective. In fact, the model suggests that these attempts at controlling experiences actually serve to increase distress. Clients are encouraged to encounter their thoughts and feelings without the aim of controlling them. Instead, they are guided to focus on leading a values-oriented life. Thus, ACT promotes experiential acceptance and a commitment to one's actions to move toward this more valued life. A recent meta-analytic review documented growing evidence for the efficacy of ACT interventions (Hayes, Luoma, Bond, Masuda, & Lillis, 2006). More recent (Forman, Herbert, Moitra, Yeomans, & Geller, 2007) examinations of the efficacy of ACT suggest that it is at least as efficacious as well-established cognitive therapies in treating depression. In their study, Forman and colleagues reported that similar to those in the CBT group, clients in the ACT intervention group exhibited large gains in clinician rated functioning, quality of life, life satisfaction, and significant reductions in depressive symptoms.

Psychodynamic Perspective

Loss and Attachment Psychodynamic theorists have proposed several causes of depression. In his classic essay of 1917, "Mourning and Melancholia," Freud (1994) likened the experience of depression to that of mourning for a lost object, either real or imagined. Although sadness is a natural response to a loss, Freud posited that depression is an overreaction to such an event. The individual is filled with conflicting feelings—love for this lost object, but simultaneously anger and resentment toward it. The anger soon turns into feelings of guilt because the individual feels responsible for the loss of the loved object and failing to live up to his or her own ideals. The depressive episode becomes a cry for love brought on by feelings of emotional insecurity (Rado, 1951). The finding that depression is frequently precipitated by life events involving interpersonal loss is consistent with this psychodynamic theory.

Another psychodynamic perspective on the etiology of depression comes from attachment theory, which offers an expansion of the idea of loss triggering depression. Bowlby (1982) and other attachment theorists proposed that the loss of an attachment figure would increase the likelihood of other stressors for the child and simultaneously decrease his or her resiliency to future adversity, which predisposes him or her to adult depression. It is also postulated that the child will have unresolved mourning due to his or her young age and inability to understand the experience of loss (Bowlby, 1980). In fact, research has shown that a strong predictor of adult depression is history of a loss between age 5 and second grade (Coffino, 2009).

Attachment theory posits that an infant's experiences with his or her caregiver will influence how he or she relates to others in the future, especially in intimate relationships (Bowlby, 1972; Hazan & Shaver, 1987). Children who view their caregiver as a secure base who will consistently respond to their distress will have better psychological outcomes such as higher self-esteem and lower levels of depression than those who have an unreliable, rejecting caregiver (Ainsworth, Blehar, Waters, & Wall, 1978). Both children and adults with this insecure attachment style tend to have higher levels of depressive symptoms than their securely attached counterparts (Kobak, Sudler, & Gamble, 1991; Muris, Meesters, van Melick, & Zwambag, 2001; Bifulco, Mahon, Kwon, Moran, & Jacobs, 2003).

Along with attachment, researchers also have focused on another important aspect of the parent–child relationship as a risk factor for depression—parenting itself. Studies have found that maternal depression is a strong predictor of childhood and adolescent depression (Hammen, Shih, & Brennan, 2004). Maternal depression decreases the quality of parenting and creates stressful life events for the family, both of which are risk factors for depression. One style of parenting, labeled "affectionless control" is characterized by low parental warmth and high psychological control, and has been shown to be an especially strong predictor of depression in children (Parker, 1983; Alloy, Abramson, Smith, Gibb, & Neeren, 2006).

Interpersonal Therapy A common theme in these psychodynamic theories is how well an individual is able to relate to others. In the 1980s, Klerman and Weissman developed interpersonal therapy based in part on this assumption (Weissman, 2006). This therapy was inspired by the work of Harry Stack Sullivan, who believed that interpersonal behaviors are of central importance to adaptive functioning as well as by the attachment theories of Bowlby. Unlike traditional psychodynamic therapy, which often is quite lengthy, interpersonal therapy is a brief therapy (lasting 12–16 sessions) that focuses on the interpersonal issues that arise in depression. It seeks to address the issues surrounding grief, interpersonal disputes, role transitions, and a lack of social skills. Studies

have shown that interpersonal therapy is an efficacious treatment for depression across the lifespan and performs as well as medication (e.g., Mufson, Weissman, Moreau, & Garfinkel, 1999; Hinrichsen, 2008).

Neuroscience Perspective Although mood disorders have a number of putative causes, including behavioral, cognitive, and environmental factors, an individual's underlying biology also significantly impacts whether he or she develops a mood disorder. In this section, we discuss genetic, neurophysiological, neuroimaging, hormonal, and neurotransmitter research on mood disorders, as well as biologically based treatments for these disorders.

Family and Genetic Studies Some of the clearest evidence for the biological contribution to mood disorders comes from research examining genetics. For example, family studies have shown that an individual's risk of developing a mood disorder increases if there is a family history of mood disorder, and that the amount of genetic material in common relates to the elevation in the risk (i.e. higher risk for those with full siblings/parents with the disorder, lower but still elevated risk for those with grandparents/aunts/uncles with the disorder). When compared with individuals with no family history of mood disorder, individuals with a first-degree relative with MDD are almost three times more likely to develop the disorder, whereas those who have a first-degree relative with bipolar disorder are almost ten times more likely to develop bipolar disorder, and the risk becomes even higher with early onset in the index case (Rasic, Hajek, Alda, & Uher, 2014; Smoller & Finn, 2003: Sullivan, Neale, & Kendler, 2000). Although it is not uncommon to find a family history of unipolar depression among those with bipolar disorder, individuals with unipolar depression typically do not have a family history of bipolar disorder (Wilde et al., 2014). This supports a conceptualization of mood disorders that specifies a unique etiology for bipolar disorder. More recent research exploring the heritability of bipolar I disorder compared with unipolar depression has shown that upwards of 71% of the genetic liability to mania is independent of the liability to depression, although bipolar II disorder may have more shared genetic factors with depression (McGuffin et al., 2003).

Twin studies and adoption studies have been used to parse the contribution of genetics and shared environment to the etiology of the disorders. Twin studies have found that concordance rates of mood disorders are higher in monozygotic twins when compared with dizygotic twins, with bipolar disorder once again evidencing a higher contribution of genetic risk. Twin studies of bipolar disorder have found heritability of bipolar diagnosis or hypomanic/manic episodes to be upwards of 75% (Kendler, 1993; Cardno et al., 1999). Adoption studies have explored the relative incidence of mood disorder onset in the biological compared with adoptive parents of children who were adopted at an early age. An early study found that 31% of adoptees with mood disorders had biological parents with a mood disorder, as compared to only 2% of adoptees who did not develop depression or mania/hypomania (Mendlewicz & Rainer, 1977). Wender and colleagues (1986) conducted a more comprehensive investigation of adoptees, their adoptive parents, and their biological parents, siblings and half siblings, and found that the prevalence of MDD was eight times greater in the biological families of depressed individuals. The same study also found that the prevalence of suicide was over 15 times greater in the biological relatives of adoptees with depression.

Genetic linkage and association studies, although not new to the field of mood disorders, have become much more prevalent, owing to the completion of the Human Genome Project and the use of genome-wide association data. These studies rely on the use of genetic sequencing to detect commonalities in populations with and without mood disorders. One of the earliest association studies examined an 81-member Amish clan with an atypically high incidence of mood pathology, primarily bipolar disorder, and found genetic abnormalities on chromosome 11 (Egeland et al., 1987). A more recent and comprehensive analysis of this population found striking diversity in genetic profiles, with no convergence of evidence implicating a common genetic pathway associated with bipolar disorder (Georgi et al., 2014). Genetic studies of mood disorders in the general population echo this finding. Meta-analyses of genetic studies have observed polymorphisms on regions on chromosomes 2, 13, and 18 associated with the transcription of a wide variety of functional proteins, including neurotransmitters, neuronal ion channels and structural components of cells (Craddock & Forty, 2006: Liu et al., 2010). It is clear that the biological contribution to mood disorders cannot be represented as a single genetic abnormality. Rather, depression and mania are most likely the result of a complex integration of multiple genetic variations with multiple psychological and environmental factors.

Many of the other putative biological variables, such as alterations in neurotransmitter function and hormonal regulation, described below, are also seen in the children of those with mood disorders, even those who have never suffered from the disorder themselves. For example, a twin study examining the stress hormone cortisol, which has been shown to be elevated in individuals with mood disorders, found that "high risk" twins (a psychopathology-free individual whose monozygotic twin had been diagnosed with a mood disorder) had higher levels of evening cortisol relative to low risk (psychopathology-free monozygotic) twins (Vinberg, Bennike, Kyvit, Andersen, & Kessing, 2008). Finally, research also has found that functional polymorphisms of neurotransmitter systems implicated in mood regulation interact with other well-established risk factors, specifically significant life stressors. Alterations in the transcription of the serotonin

transporter (responsible for recycling serotonin after its release into a synapse), the serotonin 2A receptor, tryptophan hydroxylase (an enzyme important in serotonin creation), as well as the enzyme catechol-O-methyltansferase, a chemical important in the regulation of dopamine levels within the synapse (Levinson, 2006). The functional polymorphism involving the serotonin transporter has garnered a great deal of attention after the "short" allele (the genotype that leads to the production of a less efficient serotonin transporter) was found to interact with stressful life events to precipitate depression (Caspi et al., 2003). A meta-analysis further supported the role of the 5-HTTLPR gene as a moderator of the relationship between stress and depression (Karg, Burmeister, Shedden & Sen, 2011).

Neurophysiological Research Of particular interest to neurophysiological researchers is the role that biological rhythms play in the onset and course of mood disorders. Sleep disruption is one of the most common symptoms of depression and bipolar disorder. Depressed individuals also consistently show abnormalities in their progression through the various stages of sleep (Hasler, Buysse, Kupfre, & Germain, 2010; Palagani, Baglioni, Ciapparelli, Gemignani, & Riemann, 2013; Steiger et al., 2009). One of the most documented abnormalities is shortened rapid eye movement (REM) latency. In depressed individuals, the time between sleep onset and REM onset, the stage of sleep in which dreaming occurs, is much shorter than in non-depressed individuals (Kupfer & Foster, 1972; Kupfer, 1976). Shortened REM latency is predictive of differential response to antidepressant treatment over psychotherapy, persistence of shortened REM latency beyond episode recovery, familial history of shortened REM latency and higher likelihood of relapse (Buysse & Kupfer, 1993; Giles, Kupfer, Rush, & Roffwarg, 1998). However, shortened REM latency may not be specific to depression, having also been observed in schizophrenia, panic disorder, obsessive-compulsive disorder, mania, and eating disorders (Steiger & Kimura, 2009). Sleep disruption is also a prominent feature of bipolar disorder (Harvey et al., 2005; Harvey 2008; Mehl et al., 2006).

The disruptions observed in the sleep cycles of individuals with mood disorders are suggestive of a flaw in the body's circadian system, or "biological clock." This circadian center is thought to reside in the suprachiasmatic nucleus in the brain (Cermakian & Boivin, 2003). Many believe that abnormalities in this circadian pacemaker stem from genetic variations. Shi et al. (2008) reported a significant association between the interaction of three circadian genes and bipolar disorder, suggesting that this interaction contributes to genetic vulnerability to the disorder. Moreover, Benedetti and colleagues (2007) found that individual variations in circadian genes can influence sleep and activity symptoms in mood disorders, though one study suggests that a particular gene, 3111T/C CLOCK, may only have influence over these symptoms in bipolar disorder, not unipolar depression (Serretti et al., 2010).

Circadian disruption plays a central role in the social *zeitgeber* theory of mood disorders, a biopsychosocial theory developed by Ehlers, Frank, and Kupfer (1988). Social *zeitgeber*s (translated from German as "time givers") are abundant in our everyday lives, routines, relationships, jobs, etc. These social "timing cues" are purported to possess the ability to entrain internal circadian rhythms, suggesting that disruption in social rhythms will lead to disruption in biological rhythms, resulting in affective symptoms (Ehlers et al., 1988). Life events play a crucial part in the social *zeitgeber* theory as they are thought to be the initiators of this chain of events leading to episode onset. The social *zeitgeber* theory has been most frequently applied to bipolar disorder. Shen and colleagues (2008) found significant irregularity of social rhythms among individuals with bipolar spectrum disorders, and evidence suggests individuals with bipolar disorder are more susceptible to the social rhythm-disrupting effects of life events than individuals without bipolar disorder (Boland, Bender, Alloy, Connor, & Labelle, 2012). Social rhythm irregularity has also predicted shorter time to onset of major depressive and manic/hypomanic episodes (Shen et al., 2008). Substantial research also points to disruption in circadian rhythms in depression and bipolar disorder (Leibenluft, Albert, Rosenthal, & Wehr, 1996; Kennedy, Kutcher, Ralevski, & Brown, 1996; Shi et al., 2008). Jones, Hare, and Evershed (2005) found that circadian rhythm and sleep loss patterns were less stable among participants with bipolar disorder than among those without bipolar disorder, even when the participants with bipolar disorder were not in a mood episode. Also consistent with the model, researchers have shown that stressful life events that disrupt social rhythms predict both manic and depressive episodes in bipolar disorder (Malkoff-Schwartz et al., 2000; Sylvia et al., 2009).

Treatment approaches aimed at stabilizing social and circadian rhythms have gained empirical support. Interpersonal and social rhythm therapy (IPSRT), a psychotherapy that combines elements of interpersonal therapy (described above) with a sleep and social rhythm stabilizing regimen, has been shown to increase time to relapse in individuals with bipolar I disorder (Frank et al., 2005). Additionally, participants randomized to IPSRT had higher regularity of social rhythms than those in intensive clinical management, and this regularity was significantly associated with reduced likelihood of relapse during maintenance treatment (Frank et al., 2005). IPSRT is also showing promise as a treatment for individuals with bipolar II disorder (Swartz, Frank, Frankel, Novick, & Houck, 2009), as well as adolescent samples (Hlastala, Kotler, McClellan, & McCauley, 2010) and youths at high risk for developing bipolar disorder (Goldstein et al., 2013).

Another variant of depression with strong links to biological rhythm disturbance is seasonal affective disorder, or SAD. Individuals with seasonal affective disorder experience depressive symptoms solely in the winter months. DSM-5 does not list SAD as its own separate disorder,

but rather as a "course specifier" of depression. To meet criteria for this specification, the individual has to experience this pattern of seasonality for at least 2 years, experience full remission of mood symptoms at a regular time of year, and report a history of seasonal mood episodes that outnumber non-seasonal episodes.

The predominant theory of the pathogenesis of SAD is that the disorder is precipitated by a lag in circadian rhythms, such that the individual experiences the kind of physical retardation during the day that should be taking place at night (Teicher et al., 1997; Nurnberger et al., 2000). Wehr and colleagues (2001) suggested that the circadian pacemaker, which regulates seasonal changes in behavior via the transmission of a "day length" signal to other sites in the body, may function differently in those with SAD compared with healthy individuals. Moreover, genetic studies have revealed circadian clock-related polymorphisms in SAD, with these genetic influences impacting both susceptibility to SAD, as well as diurnal preference (Johansson et al., 2003).

Roughly 75% of individuals with SAD report clinical improvements when treated with morning exposure to bright, artificial light (Oren & Rosenthal, 1992), with one study demonstrating significant effects after only 1 hour of exposure (Reeves et al., 2012) Additionally, light therapy, when applied at the first sign of seasonal symptoms, may prevent progression to a full-blown episode (Meesters et al., 1993). This preference for morning exposure has support in the literature (Lewey et al., 1998; Terman, J. S., Terman, M., Lo, & Cooper, 2001) and one study has shown a positive correlation between circadian phase advance and improvement in depressive symptoms (Terman et al., 2001). Although light therapy remains the gold standard for treatment of SAD, recent pharmacological advances have resulted in a novel antidepressant called agomelatine, which serves as both a melatonergic receptor agonist and a serotonin 2-C receptor antagonist, and has been shown to restore disrupted circadian rhythms (Koesters, Guaiana, Cipriani, Becker, & Barbui, 2013; Pirek et al., 2007; Quera Salva et al., 2007; Zupanic, & Guilleminault, 2006).

Neuroimaging Research There has been a surge in studies investigating the neural substrates of mood disorders over the past 10 years. Taken together, results from these studies implicate key brain regions thought to underlie mood disorders and their respective core domains of psychopathology. These regions include areas associated with emotion processes and mood regulation such as amygdala, cingulate gyrus, ventral striatum, and ventromedial prefrontal cortex as well as areas that play a role in memory and the encoding of affect-related information, including the hippocampus (Scoville & Milner, 1957). For example, magnetic resonance imaging (MRI) studies report amygdala abnormalities in MDD and bipolar disorder (Grotegerd et al., 2013; see Savitz & Drevets, 2009 for a review). Although reduced hippocampal volume has been consistently reported in elderly, middle-aged, and chronically ill individuals with MDD, few studies show volume reduction of this brain region in bipolar disorder. With regard to frontal and cingulate regions, volumetric decreases and functional abnormalities in orbital frontal cortex, dorsolateral prefrontal cortex, and anterior cingulate cortex have been detected in individuals with MDD and bipolar disorder. Additionally, because cortical and subcortical gray matter regions have been implicated in both MDD and bipolar disorder, recent work has also investigated white matter regions linking these areas. Frontal and subcortical white matter hyperintensities have been detected in major depression (Disabato & Sheline, 2012; Nobuhara et al., 2006) and bipolar disorder (de Asis et al., 2006; Tighe et al., 2012). Diffusion tensor imaging, an MRI technique, provides evidence of altered white matter integrity in frontal, parietal, occipitotemporal regions in MDD (Bessette, Nave, Caprihan, & Stevens, 2014; Ma et al., 2007; Yang, Huang, Hong, & Yu, 2007) as well as frontal, frontal-subcortical, corpus callosum regions in bipolar disorder (Barysheva, Jahanshad, Foland-Ross, Altshuler & Thompson, 2013; Lin, Weng, Xie, Wu, & Lei, 2011; Mahon et al., 2009; Sussman et al., 2009).

Hormone Imbalance Hormonal abnormalities also have been associated with mood disorders, specifically with bipolar and unipolar depression. Hypersecretion of cortisol is one of the most consistent and robust findings in the depression literature. Individuals with severe depression evidence hypersecretion of corticotropin-releasing hormone (CRH), exaggerated responding to adrenocoticotropic hormone, enlarged pituitary and adrenal glands, and elevated cortisol concentrations in plasma, urine, saliva, and cerebrospinal fluid (Young, 2004). One of the most frequently used assessments for HPA axis dysregulation involves the administration of dexamethasone, a glucocorticoid agonist which should inhibit cortisol production, and CRH, which should promote cortisol production. Individuals with severe or chronic depression experience what is called dexamethasone "non-suppression," meaning that after being given even very high doses of dexamethasone, their bodies fail to inhibit cortisol secretion, and their levels of circulating and salivary cortisol remain very high. Additionally, individuals with severe depression show reduced responding to CRH, suggesting that their bodies' ability to react appropriately (to promote or inhibit) to hormonal cues is severely impaired. Hypercorteoslemia, once thought to be a trait-like characteristic of depression, has subsequently been shown to abate as mood symptoms remit (Deshauer, Duffy, Meany, Sharma, & Grof, 2006), and persists only in those who are at high risk of depressive episode relapse in the immediate future (Daban, Vieta, Mackin, & Young, 2005). Cortisol hypersecretion among healthy individuals has also been shown to be a risk factor for the first onset of MDD in prospective studies (Goodyer, Herbert, Tamplin, & Altham, 2000; Harris et al., 2000).

Hypercortesolemia has been associated with impairments in learning and memory, marked hippocampal atrophy, and reductions in frontal lobe volume and impairments in functions associated with these areas (Young, 2004; Daban et al., 2005). Many of the brain areas that are negatively impacted by elevated cortisol are those which contain high concentrations of glucocorticoid receptors, lending credence to the theory that elevated cortisol is the result of impaired production/inhibition and may be the cause of many of the cognitive deficits seen in depression. There is mixed evidence as to whether hormonal abnormalities are also present during mania and hypomania, although some work has shown that irritable mania and mixed mood episodes do demonstrate cortisol abnormalities similar to those seen during a major depressive episode (Daban et al., 2005).

Other hormones, such as thyroid hormone and gonadal/ovarian hormones, have also demonstrated dysregulation in mood disorders. Research has shown that individuals with unipolar and bipolar depression have both lower basal thyrotropin and thyroid-stimulating hormone levels relative to euthymic individuals (Sassi et al., 2001; Sullivan et al., 2001). Individuals with particularly low thyroid levels have also been shown to be at greater risk of relapse (Joffe & Marriott, 2000). Additionally, a number of other studies have demonstrated a greatly increased risk for depression, mania, suicide, and even affective psychosis and psychiatric hospitalization during periods of drastic shifts in ovarian hormones (estrogen, progesterone), such as menarche, childbirth, and menopause in those individuals with a history of mood disorders (Rasgon, Bauer, Glenn, Elman, & Whybrow, 2003; Teatero, Mazmanian, & Sharma, 2014). The established influence of estrogen on important neurotransmitters such as serotonin and dopamine (Joffe, & Cohen, 1998; Kenna, Jiang, & Rasgon, 2009) could help explain its influence in mood disorders.

Neurotransmitter Dysfunction A critical element in the neurobiology of mood disorders is the manner in which the creation, release, and metabolism of neurotransmitters, particularly serotonin (5-hydroxytryptamine, or 5-HT), norepinephrine (NE) and dopamine (DA), is dysregulated. Direct studies of neurotransmitter action within a living individual are prohibitively invasive and disruptive to the individual's biochemistry; thus, evidence for dysfunction in these systems is gathered from secondary sources, such as measures of neurotransmitter metabolites in blood, alterations of the genetics regulating neurotransmitter and receptor production and functioning, and studies of the efficacy of drugs that act on certain neurotransmitter systems.

The efficacy of selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (Prozac®), sertraline (Zoloft®), and paroxetine (Paxil®) among others, have made these drugs the most common pharmacological treatment for depression, and has resulted in a great deal of research exploring the role of serotonin in mood. Research has shown that a reduction in 5-HT activity is associated with mood disorders and suicide. For example, a depletion study, in which the chemical precursor for serotonin, L-tryptophan, was experimentally reduced, resulted in depressed mood (Ruhe, Mason & Schene, 2007). Other research has shown that individuals with mood disorders have reductions in cerebrospinal fluid levels of 5-HT metabolites, suggesting they have lower levels of 5-HT in their brains (Firk & Marcus, 2007). As mentioned above, genetic research has also demonstrated that reuptake of 5-HT after release into the synapse may also be altered in those with depression, and that this alteration interacts with life stress to precipitate the onset of the disorder (Caspi et al., 2003; Kuzelova, Ptacek, & Macek, 2010). Investigations using PET found that depressed individuals show lower 5-HT receptor binding when compared with controls (Yaltham et al., 2000). Additionally, suicide completers have demonstrated alterations in 5-HT activity (Bach et al., 2014; Mann et al., 1992), including subnormal 5-HT levels and impaired 5-HT receptors in the brain stem and frontal cortex (Arango & Underwood, 1997; Meyer et al., 1999).

Catecholamines, including DA and NE, derived from the amino acid tyrosine, are thought to be critical to the phenomenology of mood disorders, particularly bipolar disorder. The DA neurons in the ventral tegmental area of the brainstem project to reward and cognition centers, such as the nucleus accumbens and the prefrontal cortex. Reductions in DA in these brain areas have been associated with blunted reward response, anhedonia, decreased motivation, and difficulties in concentration, all of which are symptoms of both unipolar and bipolar depression (Naranjo, Tremblay, & Busto, 2001). In bipolar disorder, there is evidence that DA signaling is elevated during periods of mania and reduced during periods of depression (Berk et al., 2007), and such findings are consistent with the BAS hypersensitivity model of bipolar disorder discussed above. Other evidence for the role of DA in bipolar disorder includes the phenomenological similarities between mania/hypomania and amphetamine use (amphetamines increase dopamine in the synapse), high rates of comorbidities with bipolar disorder and other disorders impacted by DA (such as ADHD and substance abuse), structural abnormalities in dopaminergic brain structures in those with bipolar disorder, reduced CSF levels of DA metabolites (suggesting reduced DA volume), increased activity of enzymes responsible for DA breakdown (such as catechol-O-methyltransferase) and decreased DA receptor binding in individuals with bipolar disorder (Cousins, Butts, & Young, 2009). All of these findings suggest that individuals with bipolar disorder may possess physical alterations to dopaminergic brain structures, reduced DA release, increased rates of DA breakdown when it is released, and impaired signaling when DA reaches the post-synaptic receptor.

Early studies posited a central role of NE, due in large part to the findings that experimentally increased levels of NE produce mania, whereas decreased levels produce

depression (Schildkraut, 1965; Delgado & Moreno, 2000). Additionally, many of today's novel antidepressants, such as buproprion (Wellbutrin®) and venlafaxine (Effexor®), target NE signaling and disrupt reuptake of released neurotransmitter into the presynaptic neuron (Nutt et al., 2007). There is also evidence that other effective treatments, such as electroconvulsive therapy (ECT) may act by increasing the bioavailability of DA and NE (Nutt, 2006). A meta-analysis of monoamine depletion studies found that depletion of 5-HT, DA and NE results in slightly lowered mood in those individuals with a family or personal history of depression, but not in normal controls (Ruhe et al., 2007). The authors of this analysis suggest that reductions in the bioavailability of these monoamines probably represents a vulnerability to depression which then interacts with other environmental, social, and biological risk factors to actually lead to depression.

In addition to traditional neurotransmitter models of major depressive and bipolar disorder, there has also been investigation into other neurochemicals, such as glutamate, gamma aminobutyric acid, a variety of neuropeptides, and cell-signaling molecules, which may play a role in dysregulated affect (Kugaya & Sanacora, 2005). Pharmaceutical interventions targeting these novel neurobiological candidates are currently being explored (Matthew, Manji, & Charney, 2008). Finally, changes in plasticity (a neuron's ability to grow or shrink) and neuroarchitecture can result from treatment with antidepressants and mood stabilizers, and are also theorized to play an important role in mood disorders (Sanacora, 2008; Frey et al., 2007).

Psychopharmacology Whatever the neuroscience perspective ultimately explains about the causes of mood disorders, it has contributed importantly to their treatment in the form of antidepressant and antimanic medications. The primary classes of antidepressant medication include the monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, tetracyclic antidepressants, SSRIs, and serotonin-norepinephrine reuptake inhibitors (SNRIs). Newer types of antidepressants include noradrenergic and specific serotonergic antidepressants, norepinephrine reuptake inhibitors, norepinephrine–dopamine reuptake inhibitors, selective serotonin reuptake enhancers, and norepinephrine–dopamine disinhibitors. Each of these classes seems to work by acting on certain neurotransmitters. For example, MAOIs interfere with an enzyme that breaks down 5-HT, DA and NE; tricyclics block the reuptake of 5-HT and NE; tetracyclics increase levels of NE and 5-HT; SSRIs block the reuptake of 5-HT; and the SNRIs inhibit the reuptake of 5-HT and NE.

The choice of antidepressant depends on which drug provides the greatest symptom relief with the fewest adverse effects (Zimmerman et al., 2004). Additionally, treatment history, co-occurring psychiatric disorders, and particular clinical symptoms also should be taken into account. MAOIs, one of the older classes of antidepressant drugs, demonstrate higher levels of adverse effects, and are thus typically only prescribed for select manifestations of depression (i.e., "atypical depression") or when other medications prove ineffective (McGrath et al., 2000). Tricyclics, the oldest class of antidepressant medication, can also have negative side effects, including drowsiness, sexual dysfunction, blurred vision and increased heart rate. Moreover, given their toxicity (ten times normal dosages), it is easy to overdose on tricyclics and thus, they must be prescribed with caution to suicidal patients. Nonetheless, they have been shown to be significantly more effective than placebo (Arroll et al., 2005).

Clinicians perceive the newer medications (e.g. SSRIs and SNRIs) to be more effective than older classes of antidepressants (Petersen et al., 2002); thus, they have gradually displaced most other antidepressants. Importantly, however, efficacy of SSRIs for the treatment of depression remains controversial, as some studies report superior efficacy over placebo (Hollon, DeRubeis, Shelton, & Weiss, 2002; Thase, 2002), whereas others report that they may not be much more effective than placebos (Kirsch, moore, Scoboria, & Nicholls, 2002). Two meta-analyses of clinical trials reported a small effect in mild and moderate depression, but a more robust effect in severe depression (Fournier et al., 2010; Kirsch et al., 2008). Further, SSRIs have the added advantage of fewer adverse effects than tricyclics, and they act more quickly. Emerging research into novel antidepressant treatments have demonstrated that administration of ketamine, an anesthetic neurochemical that mimics glutamate and acts on N-methyl-D-aspartate receptors, is associated with a rapid and sustained antidepressant effect on treatment-resistant and refractory depression (Machado-Viera, Salvadore, Diazgranados & Zarate, 2009). Further studies are needed to explore whether ketamine, or other glutamatergic agonists, could represent viable medical interventions for depression.

There is also a long-standing debate about whether pharmacotherapy or psychotherapy is a more effective approach to treating depression. Recent work comparing the two types of treatment found that antidepressants are as effective as psychotherapy for MDD, whereas medication yields better results for dysthymic disorder (Cuijpers, van Straten, van Oppen, & Andersson, 2008; Imel, Malterer, McKay, & Wampold, 2008). Further, SSRIs may be more efficacious than psychotherapy treatment initially, but more patients have been shown to discontinue antidepressants, as compared with those in psychotherapy, perhaps due to adverse medication effects. Moreover, as discussed earlier, psychotherapies such as behavioral activation and CBT have been found to reduce relapses and recurrences of depression.

For bipolar disorder, mood stabilizer medications, particularly lithium, are typically the first choice of pharmacological treatment. Antidepressants have also been used to treat bipolar disorder, but some work reports potential triggering of rapid cycling and, in some cases, initiation of manic, hypomanic, or mixed episodes (Harel & Levkovitz,

2007). Individuals with bipolar disorder who take antidepressants are typically prescribed a mood stabilizer as well (Sachs et al., 2007).

Aside from lithium, most of these medications are anticonvulsants, such as sodium valproate (Macritchie et al., 2002). For patients with bipolar disorder experiencing more severe manic or mixed episodes, either lithium plus an antipsychotic is typically prescribed, or valproate plus an antipsychotic. For patients with less severe symptoms, lithium, valproate or an antipsychotic are prescribed. Lithium is among the most commonly prescribed mood-stabilizing medications for bipolar disorder. It works to control manic symptoms and prevent relapses of manic and depressive episodes. Nonetheless, it is important to note the difficulty in determining the maintenance dose, primarily because, often, the effective dose is close to the toxic dose, which may lead to convulsions, delirium and, in rare instances, death. Typically, an individual who has overdosed will experience warning signs, such as nausea, which tell them they should discontinue use. One additional complication with lithium is that patients who stop taking it after approximately 2 years may experience a new depressive or manic episode and increased risk of suicide (Baldessarini, Tondo, & Viguera, 1999). As a result of these potential dangers associated with lithium, alternative treatment options have been introduced, including use of anticonvulsants, such as valproate, lamotrigine, gabapentin, topiramate, carbamazepine, and oxcarbazepine. Various psychotherapies are often used as an adjunctive treatment along with pharmacotherapy (Nusslock et al., 2009).

Electroconvulsive Therapy Another long-standing biological treatment for mood disorders is ECT. Electric shock, when applied to the brain under controlled circumstances, has been shown to ameliorate symptoms of severe, refractory depression. ECT is conducted by administering a shock of approximately 70–130 volts directly to the patient's brain, resulting in a convulsion similar to a seizure. The treatment is typically administered approximately nine or ten times, spaced over the period of several weeks. The patient is generally hospitalized prior to treatment and is anesthetized throughout the procedure.

ECT was first developed in the 1930s, and although it is clear that ECT does work (Bailine et al., 2000; Cohen et al., 2000), it is still relatively unclear how it works. Yatham and colleagues (2010) found that ECT functions to downregulate 5-HT receptors, much in the same way as antidepressants. However, ECT is capable of further downregulating the 5-HT receptors in individuals with treatment-resistant depression, thus perhaps shedding some light on why it is often efficacious in this difficult to treat subset of patients.

ECT is not without complications, however. The most common adverse effect is memory dysfunction, both anterograde (learning new material after treatment) and retrograde (recalling material from before treatment) amnesia. Anterograde memory deficits are temporary (Hay & Hay, 1990; Criado, Fernandez, & Ortiz, 2007), though retrograde memory deficits take longer to resolve, with most experiencing a marked loss 1 week following treatment, and a nearly complete recovery within 7 months post treatment. Longer-term studies of up to 12 years of follow-up suggest that few cognitive impairments remain (Elias, Chathanchirayil, Bhat, & Prudic, 2014). In many cases, however, some subtle memory losses persist beyond the typical 7-month post-treatment period, particularly for events that occurred in the 1-year period prior to treatment, and particularly for interpersonal events (Lisanby, Maddox, Prudic, Devanand, & Sakeim, 2000). ECT confined to one hemisphere of the brain (ideally the right hemisphere), or ECT focused on the frontal rather than the temporal lobes, is associated with decreased risk for cognitive impairment following treatment (Sackeim et al., 2000; Bailine et al., 2000).

A newer biological treatment for depression uses powerful magnetic fields to restore dysfunctional brain activity in depressed individuals. Transcranial magnetic stimulation (TMS) involves placing an electromagnetic coil on the scalp through which high-intensity current produces a brief magnetic field that induces electrical current in neurons, thus resulting in neural depolarization (George, Lisanby, & Sackeim, 1999). This is the same depolarization effect seen in ECT. An advantage of TMS lies in its ability to apply more finely tuned stimulation than ECT. Although occasional mild headache and discomfort at the stimulation site has been reported, patients receiving TMS generally report no other adverse side effects (George et al., 1999). The method has been approved for treatment-resistant depression in several countries, but it has yet to gain approval in the United States, largely due to the Food and Drug Administration's concerns about its efficacy (Marangell, Martinez, Jurdi, & Zboyan, 2007). Tests of TMS using a sham control have yielded conflicting results and have been difficult to compare, owing to non-standardized stimulation methods, thus making the true efficacy of the treatment difficult to determine (Burt, Lisanby, & Sackeim, 2002; Marangell et al., 2007). Moreover, a recent meta-analysis has shown ECT to be more effective than TMS in treating depression (Berlim, Van den Eynde, & Daskalakis, 2013).

Conclusion

Although they have been recognized and studied for centuries, mood disorders still remain something of a mystery. Although major advances in the understanding and treatment of mood disorders have been made over the last several decades, there are still gaps in our knowledge of these conditions. As discussed in this chapter, many different potential causes and treatments for the mood disorders have been suggested from a variety of theoretical perspectives. More recent theoretical models, such as the BAS hypersensitivity model or social *zeitgeber* theory,

for example, have attempted to integrate research across multiple perspectives. It is likely that a full understanding of the causes of mood disorders will require even further integration of cognitive, behavioral, psychosocial, and neurobiological mechanisms in the future.

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