Psychological Disorders

14

After reading this chapter, you will be able to:

• Name and describe the various categories of psychological disorders.
• Understand characteristics and neurological causes of schizophrenia.
• Describe how heredity and environment interact to produce psychological disorders.
• Understand the symptoms and causes of the affective disorders.
• Understand and describe the symptoms and physiological causes of the anxiety disorders.
• Explain the causes and features of the various personality disorders.

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Ob Garrett stood by his chair and waited for the students to take their places around the table, eagerly tying up the loose ends of conversations that the trek across campus hadn’t given them time to finish. As the bell in the East College tower tolled the start of the hour and he was about to call the class to order, Ned got up from his seat and approached him.

“I forgot to give the bookstore cashier her pen after I used it to write a check. Can I take it back?”

“I think she can wait until class is over,” he answered. Ned accepted that judgment and returned to his seat, but he seemed restless for the remainder of the hour. As soon as class was over, he was one of the first out of the door. Bob couldn’t help but smile at Ned’s youthful impetuosity.

“Canst thou not minister to a mind diseas’d? Pluck from the memory a rooted sorrow. Raze out the written troubles of the brain.”

—William Shakespeare, Macbeth
The next day he understood that Ned's behavior had a completely different origin. Around 10 o'clock the night before, his dorm mates found him huddled on the stair landing, fending off an imaginary alien spaceship circling over his head and firing projectiles at him. He was taken to the hospital and sedated; then his parents took him back to his hometown, where he spent several months in a hospital psychiatric ward. He was diagnosed with paranoid schizophrenia. Fortunately, medication helped, and he was able to move to a home school with a comprehensive program of support and rehabilitation.

Ned has now spent two thirds of his life at the home. A few years ago he wrote to Bob, and they have kept up a regular correspondence since; his primary motivation is that he remembers his brief time in college as the happiest in his life. It is not that the home is unpleasant. He is on the baseball, basketball, and golf teams; he works part time outside the home; and he has a girlfriend. Questions he asks in his letters reveal a healthy curiosity, usually provoked by something he has read or seen on television about the brain. Once he talked candidly about his diagnosis, and about how he prefers to believe that someone slipped him a dose of LSD on that fateful night. There is no evidence that happened, but even if it did, it only precipitated, rather than caused, the decades-long debilitation that followed. Despite Ned’s apparently good adjustment—and we see only the face that he wants to put on his situation—the preadolescent intellectual maturity of his letters and the barely legible scrawl of his handwriting suggest the havoc that schizophrenia has wreaked in his brain. Ned is unable to function outside the home’s protective environment and professional support, and he will never be able to leave.

Researchers estimate that one out of every four adults in the United States suffers from a diagnosable mental illness, and that 46% will fall victim during their lifetime (R. C. Kessler et al., 2005). We aren’t sure how many people are mentally ill, because researchers rely primarily on self-reports, which are notoriously

### TABLE 14.1 Mental Disorders.

<table>
<thead>
<tr>
<th>DISORDER</th>
<th>SYMPTOMS</th>
</tr>
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<tbody>
<tr>
<td>Schizophrenia</td>
<td>Perceptual, emotional, and intellectual deficits; positive and negative</td>
</tr>
<tr>
<td></td>
<td>symptoms</td>
</tr>
<tr>
<td>Affective Disorders</td>
<td></td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>Sadness, hopelessness, decreased enjoyment, loss of energy and appetite,</td>
</tr>
<tr>
<td></td>
<td>slow thought, sleep disturbance</td>
</tr>
<tr>
<td>Bipolar disorder*</td>
<td>Alternating depression and either anxiety, irritation, or mania</td>
</tr>
<tr>
<td>Seasonal affective disorder</td>
<td>Depression that worsens in the winter and improves in the summer</td>
</tr>
<tr>
<td>Anxiety, Trauma, and Stress-Related Disorders</td>
<td></td>
</tr>
<tr>
<td>Generalized anxiety disorder</td>
<td>Feeling of stress and unease most of the time</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>Sudden and intense attack of anxiety with no obvious trigger</td>
</tr>
<tr>
<td>Phobia</td>
<td>Fear or stress when confronted with a particular situation</td>
</tr>
<tr>
<td>Posttraumatic stress disorder</td>
<td>Prolonged stress reaction to a stressful event characterized by recurrent</td>
</tr>
<tr>
<td></td>
<td>thoughts, images, nightmares, impaired concentration, and overreaction</td>
</tr>
<tr>
<td></td>
<td>to sudden events</td>
</tr>
<tr>
<td>Personality Disorders</td>
<td></td>
</tr>
<tr>
<td>Obsessive-</td>
<td>Recurrent, uncontrollable thoughts (obsessions) paired with ritualistic</td>
</tr>
<tr>
<td>compulsive disorder</td>
<td>behaviors that remove anxiety (compulsions)</td>
</tr>
<tr>
<td>Tourette syndrome</td>
<td>Involuntary motor and sound tics, grimaces, blinks, grunts, and imitation</td>
</tr>
<tr>
<td>Borderline personality disorder</td>
<td>Unstable mood, self-image, anxiety, self-harm, and anger that leads to</td>
</tr>
<tr>
<td></td>
<td>impulsive acts due to apparently common events</td>
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</tbody>
</table>
Chapter 14: Psychological Disorders

inaccurate. In late-life interviews people recalled bouts of mental illness 2–12 times less often, depending on the type of illness, than they had reported them in three interviews over the previous 25 years (Takayanagi et al., 2014). The monetary cost in terms of treatment and lost wages amounts to $467 billion a year in the United States (Insel, 2015) and $2.5 trillion globally (Trautmann, Rehm, & Wittchen, 2016). According to the World Health Organization (2008), mental disorders are the leading cause of disability among people aged 15 to 44 in the United States and Canada (Figure 14.1). An obvious benefit of research is the development of improved therapeutic techniques; in addition, because the disorders involve malfunctions in neurotransmitter systems and brain structures, studying them helps researchers understand normal neural functioning as well. In this chapter, we will make good use of what you have already learned about brain structure and neurotransmitter activity as we examine schizophrenia, mood disorders, and anxiety disorders, and in turn this survey will further expand your knowledge of how the brain works.

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5; American Psychiatric Association, 2013), provides the framework for therapists, clinicians, and researchers in assessing an individual's unique history and symptoms and arriving at a diagnosis from a long list of disorders (for example, see Table 14.1). Many of these disorders have been discussed in prior chapters, such as substance-related disorders (Chapter 5), eating disorders (Chapter 6), sexual and gender dysfunctions (Chapter 7), aggressive and disruptive disorders (Chapter 8), and neurodevelopmental and cognitive disorders (Chapters 12 and 13). This chapter will focus on several of the remaining disorders: schizophrenia spectrum disorders, affective disorders, anxiety disorders not covered in Chapter 8, and obsessive-compulsive disorders.

Schizophrenia

Schizophrenia is a debilitating disorder characterized by perceptual, emotional, and intellectual deficits; loss of contact with reality; and inability to function in life. Schizophrenia is a psychosis, which simply means that the individual has severe disturbances of reality, orientation, and thinking. Schizophrenia is the most severe of the mental illnesses, and it is particularly feared because of the bizarre behavior it produces in many of its victims. All social classes are equally vulnerable; though patients themselves “drift” to lower socioeconomic levels, when they are classified by their parents’ socioeconomic level, the classes are proportionately represented (Huber, Gross, Schütter, & Linz, 1980). Schizophrenia is diagnosed in about 1% of the population worldwide; in the United States the rate is 1.2%, or roughly 3.8 million people (Nemade & Dombeck, 2009). The economic burden of schizophrenia amounts to $156 billion annually in the United States, which included direct health care costs (24%), unemployment (38%), and caregiving (34%) (Cloutier et al., 2016). Fortunately, schizophrenia is one of the few psychological disorders that appear to be on the decline. Critics have attributed the apparent reduction to methodological flaws in studies, but a study of all people born in Finland between 1954 and 1965 found a significant decline in each successive age-group, totaling 29% for women and 33% for men (Suvisaari, Haukka, Tanskanen, & Lönnqvist, 1999). This decrease has been noted in other countries such as Canada (Woogh, 2001) and Japan (Toshitani et al., 2006), but as of 2017 there hasn’t been a systematic study in the United States.

Characteristics of the Disorder

The term schizophrenia was coined in 1911 by the Swiss psychiatrist Eugen Bleuler (Figure 14.2) from the combination of two Greek words meaning “split mind.” Contrary to popular belief, schizophrenia has
nothing to do with multiple personalities; the term refers to the distortion of thought and emotion, which are "split off" from reality. The schizophrenic has some combination of several symptoms: hallucinations (internally generated perceptual experiences, such as voices telling the person what to do); delusions (false, unfounded beliefs, such as that one is a messenger from God); paranoia, characterized by delusions of persecution; disordered thought; inappropriate emotions or lack of emotion; and social withdrawal. Note that Ned had a hallucination of a spaceship, the paranoid delusion that it was attacking him, and a possible delusion about the LSD.

In the past, people with schizophrenia were subdivided into diagnostic categories based on which of these symptoms was predominant, such as paranoid or catatonic. However, patients often have overlapping symptoms and can receive multiple diagnoses, so there is little belief that these categories represent distinct disease processes. Also, as neuroscience and evidence-based practices progress, we are realizing that two people can have the same symptom with different causes or the same brain defect with different symptoms. As a result, the National Institute of Mental Health encourages researchers to shift their focus from diagnostic categories to underlying neural and genetic mechanisms (G. Miller, 2010). As a first step in that direction, the DSM-5 eliminated these subgroups of schizophrenia as diagnostic categories (American Psychiatric Association, 2013).

Schizophrenia afflicts men and women about equally often, and there is no difference in incidence between urban and rural environments (Saha, Chant, & McGrath, 2005). Men usually show the first symptoms during their teens or twenties, as Ned did, while the onset for women ordinarily comes about a decade later (Figure 14.3). Acute symptoms develop suddenly and are typically more responsive to treatment; the prognosis is reasonably good despite brief relapses. Symptoms that develop gradually and persist for a long time with poor prognosis are called chronic. The media has frequently overplayed the bizarre features of schizophrenia; many patients are able to function reasonably well, especially if they are fortunate enough to be among those who respond to antipsychotic drugs. Among patients studied 20 years after their first psychiatric admission, 22% were fully recovered, another 43% were improved, and the symptoms of the remaining 35% had remained the same or worsened; 56% were fully employed (Huber et al., 1980). A more recent meta-analysis of over 114 studies performed by Warner (2005) is consistent with this earlier study (20%–25% fully recovered).

In the late 1700s and early 1800s, doctors began to view mental illness as a medical problem; at that time, the mentally ill were literally released from their chains and given treatment (Figure 14.4; Andreasen, 1984). By the early 20th century, it was widely assumed that schizophrenia had a physiological basis. But when the search for biological causes produced little success, the emphasis shifted in the 1940s to the social causes of schizophrenia, especially in America, where Freud’s theory of psychoanalysis was in its ascendancy and biologically oriented psychiatrists were in the minority (Andreasen; Wender, Rosenthal, Kety, Schulsinger, & Welner, 1974). Until the 1960s, research techniques were not up to the task of demonstrating the validity of the physiological position. It was then that increasing knowledge of neurotransmitters, the advent of brain scanning techniques, and improved genetic studies shifted the explanation for schizophrenia back to the realm of biology and permanently changed the perception of mental illness.
I'm a paranoid schizophrenic and for us life is a living hell. . . . Society is out to kill me. . . . I tried to kill my father. I went insane and thought he ruled the world before me and caused World War Two.
—Ross David Burke in When the Music's Over: My Journey Into Schizophrenia

FIGURE 14.4 Philippe Pinel Freeing Mental Patients From Their Chains.

Patients were warehoused without treatment; sometimes care consisted of throwing in fresh straw and food once a week. Pinel was convinced that they would benefit from humane treatment and in 1794 freed the mental patients of Paris from their chains.

Source: © Rapho Agence/Photo Researchers.

Hereditry

Schizophrenia is a familial disorder, which means that the incidence of schizophrenia is higher among the relatives of people with schizophrenia than it is in the general population (Gottesman, McGuffin, & Farmer, 1987; Tsuang et al., 1991). Of course, this association could be due to environmental influence or to heredity; in fact, in the 1940s supporters for both the genetic and environmental bases argued for their positions from the same data (Wender et al., 1974). However, studies of twins and adoptees provided compelling evidence for a genetic influence.

Twin and Adoption Studies

In Figure 14.5, you can see that the shared incidence of schizophrenia increases with the genetic closeness of the relationship and that the concordance rate for schizophrenia is three times as high in identical twins as in fraternal twins (Lenzenweger & Gottesman, 1994). In other words, identical twins of people with schizophrenia are three times as likely to develop the disorder as the fraternal twins of patients. The heritability for schizophrenia has been estimated at between .60 and .90 (Tsuang et al., 1991). This means that 10%–40% of the variability is due to environmental factors.

Information from adoption studies gives a more impressive indication of genetic influence; these studies show that adopting out of a home with schizophrenia provides little or no protection from developing schizophrenia symptoms. The incidence of schizophrenia and schizophrenia-like symptoms was 28% among individuals adopted out of Danish homes in which there was one parent with schizophrenia, compared with 10% in matched adoptees from homes without an individual with symptoms (Lowing, Mirsky, & Pereira, 1983). Other studies have produced similar findings.

Discordance among identical twins has been used as an argument that schizophrenia is environmentally produced. To address this issue, Gottesman and Bertelsen (1989) compared the incidence of schizophrenia in the offspring of affected and normal identical twins; they found that the offspring of the
FIGURE 14.5 Concordances for Schizophrenia Among Relatives.

<table>
<thead>
<tr>
<th>Genetic Relatedness</th>
<th>Relationship</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>Identical twin</td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td>Offspring of two patients</td>
<td>46%</td>
</tr>
<tr>
<td>50%</td>
<td>Fraternal twin</td>
<td>17%</td>
</tr>
<tr>
<td>50%</td>
<td>Offspring of one patient</td>
<td>17%</td>
</tr>
<tr>
<td>50%</td>
<td>Sibling</td>
<td>9%</td>
</tr>
<tr>
<td>25%</td>
<td>Nephew or niece</td>
<td>4%</td>
</tr>
<tr>
<td>0%</td>
<td>Spouse</td>
<td>2%</td>
</tr>
<tr>
<td>0%</td>
<td>Unrelated person in the general population</td>
<td>1%</td>
</tr>
</tbody>
</table>


unaffected identical twins were just as likely to be schizophrenic as the offspring of the affected twins (Figure 14.6). This result would not have occurred unless the normal twins were carrying genes for schizophrenia. Discordance does raise the question, however, of whether some environmental factors determine whether the person's schizophrenic genes will remain "silent." Refer back to Chapter 6 for the discussion of these epigenetic effects on genes.

The Search for the Schizophrenia Genes

Although we have known for a long time that schizophrenia is partially genetic, identifying the genes involved has been difficult. One reason has been researchers' inconsistency in including the spectrum disorders in their diagnosis of schizophrenia (Heston, 1970; Lowing et al., 1983). When identical twins are discordant for schizophrenia, 48%–54% of the nonschizophrenic twins have spectrum disorders (Heston; Onstad, Skre, Tørgersen, & Kringlen, 1991). If the spectrum disorders are due to the same genes, then classifying these individuals as nonschizophrenic means that the genes will not appear to distinguish between schizophrenia and normality. A second problem is that schizophrenia apparently involves the cumulative effects of multiple genes, each of which has a small effect by itself. Evidence indicates that the number of variants contributing to schizophrenia is in the thousands (Wray & Visscher, 2010). A person's risk of schizophrenia presumably increases with the number of these genes inherited. This view is supported by the fact that risk has been found to increase with the number of relatives who are schizophrenic and with the degree of the relatives' disability (Heston, 1970; Kendler & Robinette, 1983).

Recent genome-wide studies have identified at least 108 genes suspected of a role in producing schizophrenia (Schizophrenia Working Group, 2014). These genes are typically related to neurodevelopment and plasticity, neurotransmission (such as dopamine, glutamate, and calcium channels), immune responses, and hormonal activity, such as the DISC1 (disrupted in schizophrenia 1) gene. This gene appears to change how neurons develop and migrate by disrupting a messenger system in neurons in areas involved in learning, memory, and mood (J. Y. Kim et al., 2009; Millar et al., 2000; Millar et al., 2005). Although many genes such as DISC1 have been linked to schizophrenia, they have small individual effects and together may account for less than 5% of the variability in susceptibility. Copy number variations (CNVs) have much larger effects; for example, a duplication of a segment of DNA on chromosome 7 produces a 10-fold increase in risk (Mulle et al., 2014). But CNVs are individually rare and make an even smaller contribution than common genes. The large majority of CNVs are inherited, but de novo mutations are more often implicated in diseases. Along with epigenetic modifications, they help account for discordance in identical twins, who otherwise have identical genomes. Epigenetic studies of schizophrenia are in their infancy. Though they have produced interesting results, our knowledge is based on small numbers of subjects and tissues taken from widely varying brain locations. According to one group of reviewers, some of the current results may be harder to interpret than early small-sample gene association studies (Dempster, Viana, Pidsley, & Mill, 2013).

Schizophrenia is a very old disease (see W. J. Ray, 2014, for a review). Disorders with psychotic-like symptoms have been reported for 4,000 years, and similar rates in disparate and long-separated societies suggest that the genes were present before humans left Africa some 100,000 years ago. So why wouldn't genes as detrimental as those that produce schizophrenia be eliminated through evolution? One suggestion is that the genes that in combination can produce schizophrenia individually confer an evolutionary
advantage. Ten or fifteen centuries ago, these individual genes might have helped individuals cope with the demands of burgeoning social culture. It has been pointed out that many gifted Nobel recipients, the likes of Albert Einstein, Bertrand Russell, and John Nash (featured in the film *A Beautiful Mind*), either had some schizophrenic traits or had relatives thought to have schizophrenia. In addition, an individual’s overall risk for schizophrenia (as well as for bipolar disorder) is highly correlated with intellectual and artistic creativity (Power et al., 2015). Therefore, our amazing human ability to express, integrate, and create comes with an increased risk for psychotic disorders that can be triggered by the same genes and circuits.

### The Vulnerability Model

Most researchers agree that genes determine only the person’s vulnerability for the illness; both heredity and environment are needed to explain the etiology (causes) of schizophrenia (Zubin & Spring, 1977) as well as most other disorders. According to the vulnerability model, some threshold of causal forces must be exceeded for the illness to occur; environmental challenges combine with a person’s genetic vulnerability to exceed that threshold. The environmental challenges may be external, such as bereavement, job difficulties, or divorce, or they may be internal, such as maturational changes, poor nutrition, infection, or toxic substances. There is mounting evidence that these environmental influences work in part by epigenetic means, that is, by upregulating and downregulating gene functioning (Tsankova, Renthal, Kumar, & Nestler, 2007). Vulnerability is viewed as a continuum, depending on the number of affected genes inherited. At one extreme, a small percentage of genetically predisposed individuals will become schizophrenic under the normal physical and psychological stresses of life; at the other extreme are individuals who will become schizophrenic only under the severest stress such as the trauma of battle (Fowles, 1992) or because of a constantly stressful life with poor social support and family environments (see Lange et al., 2017).

### Two Kinds of Schizophrenia

Researchers disagree on whether schizophrenia represents one disease or many, but most authorities do agree that the symptoms fall into two major categories: positive and negative. Positive symptoms involve the presence or exaggeration of behaviors, such as delusions, hallucinations, disorganized thinking, and abnormal motor behaviors. Negative symptoms are characterized by the absence or insufficiency of normal behaviors and include lack of affect (emotion), inability to experience pleasure, lack of motivation, poverty of speech, and impaired attention and social interactions.

Crow (1985) theorized that positive and negative symptoms are due to two different syndromes of schizophrenia, with different causes and different outcomes. His Type I and Type II schizophrenias are described in Table 14.2. Subsequent research has supported this distinction in many respects. Positive symptoms are more often acute, and they are more likely to respond to antipsychotic drugs than are negative symptoms (Fowles, 1992). Negative symptoms tend to be chronic; these patients show poorer adjustment prior to the onset of the disease (Andreasen, Flaum, Swayze, Tyrrell, & Arndt, 1990); poorer prognosis after diagnosis (Dollfus et al., 1996); more intellectual and other cognitive deficits, suggestive of a brain disorder (Andreasen et al., 1990); and greater reduction in brain tissue (Fowles). These findings led researchers to think in terms of two distinct groups of patients, a view we will modify shortly.

![FIGURE 14.6 Risk of Schizophrenia in the Offspring of Normal and Schizophrenic Twins.](image-url)

Offspring of the normal fraternal twin of a schizophrenic do not have an elevated risk. The offspring of the normal identical twin of a schizophrenic are as likely to become schizophrenic as the offspring of the schizophrenic identical twin.

Source: Based on data from Gottesman and Bertelsen (1989).

*What consoles me is that I am beginning to consider madness as an illness like any other, and that I accept it as such.*

—Vincent van Gogh, 1889, in a letter to his brother, Theo
The Dopamine Hypothesis

Little could be done to treat psychotic patients until the mid-1950s, when a variety of antipsychotic medications arrived on the scene. For the first time in history, the population of hospitalized mental patients decreased in size. As is often the case in medicine, and more particularly in mental health, these new drugs had not been designed for this purpose—researchers had too little understanding of the disease to do so. Doctors tried chlorpromazine with a wide variety of mental illnesses because it calmed surgical patients, and it turned out to help those with schizophrenia as well. However, it was not clear why chlorpromazine worked, because tranquilizers have little or no usefulness in treating schizophrenia.

So, investigators tried reverse engineering. You will remember from Chapter 5 that amphetamine overdose causes psychotic behavior indistinguishable from schizophrenia, complete with hallucinations and paranoid delusions. In time, researchers determined that amphetamine produces these symptoms by increasing dopaminergic activity. This discovery eventually led to the dopamine hypothesis, that schizophrenia involves excessive dopamine activity in the brain. According to the theory, blockade of the D₂ type of dopamine receptors is essential for a drug to have an antipsychotic effect, and a drug's effectiveness is directly related to the drug's blocking potency. The theory has considerable support; schizophrenic patients typically have higher dopamine activity in the striatum (Abi-Dargham et al., 2000), and drugs that block dopamine receptors are effective in treating the positive symptoms of schizophrenia (S. H. Snyder, Bannerjee, Yamamura, & Greenberg, 1974). In fact, the effective dosage for most antipsychotic drugs is directly proportional to their ability to block dopamine receptors (Figure 14.7; Seeman, Lee, Chau-Wong, & Wong, 1976). What exactly does dopamine do to trigger the symptoms of schizophrenia? One theory, called the aberrant salience hypothesis, suggests that heightened levels of dopamine increase attentional and motivational circuits to make ordinary environmental features seem significant. Therefore, an individual projects his or her own thoughts and imaginings as real-world events and experiences (Howes & Nour, 2016).

Beyond the Dopamine Hypothesis

However, the drugs did not help 30%–40% of schizophrenic patients, and—troublesome for the dopamine theory—nonresponsive patients experienced just as much D₂ receptor blockade as responders. In fact, in some of them the blockade exceeded 90%, while some responders showed remarkably low levels of receptor blocking (Kane, 1987; Pilowsky et al., 1993). Furthermore, some patients appear to have a dopamine deficiency, especially those with chronic, treatment-resistant symptoms (Grace, 1991; Heritch, 1990; Okubo et al., 1997).

Another problem for the drugs was that the side effects could be permanently disabling. Prolonged use of antidopamine drugs often produces tardive dyskinesia, tremors and involuntary movements due to long-term blocking of dopamine receptors and resultant neuron death in the basal ganglia. Once dyskinesia
develops, it persists even after the person stops taking the drug. Seventy years ago, this effect was believed to be so inevitably linked to the therapeutic benefit that the “right” dose was the one that caused some degree of motor side effects. Thus, the drugs used to treat schizophrenia became known as neuroleptics, because the term means “to take control of the neuron” (Julien, 2008). The effect appears to be due to a compensatory increase in the sensitivity of D2 receptors in the basal ganglia. (This is a good illustration of the fact that drugs do not affect just the part of the brain we want to treat.)

Since the early 1990s, we have seen the introduction of several new antipsychotic substances that are referred to as atypical or second-generation drugs. Atypical antipsychotics block D2 receptors less strongly, while also targeting non-dopamine receptors; as a result, they produce motor problems only at much higher doses, but they still reduce psychotic symptoms. Fortunately, avoiding motor side effects does not require a therapeutic compromise. The major atypical antipsychotics are at least equivalent to the first-generation drugs, and some are 15%–25% more effective; what is more, they often bring relief to treatment-resistant patients (Iqbal & van Praag, 1995; Pickar, 1995; Siever et al., 1991). So, is the dopamine hypothesis just another example of a beautiful hypothesis slain by ugly facts? Not entirely; although atypical antipsychotics mostly target other receptors, those that lack at least a modest effect at D2 receptors are therapeutically ineffective (H. M. Jones & Pilowsky, 2002). So, successful therapy apparently requires D2 blockade and other effects. For a summary of the types of drugs prescribed for individuals with schizophrenia, and their side effects, see the accompanying Research Spotlight.

And what are these other effects? One involves serotonin. The serotonergic system is suspect largely because of the 5-HT2A receptor’s involvement in schizophrenic-like responses to hallucinogenic drugs, such as psilocybin and LSD. The number of 5-HT2A receptors is upregulated in the brains of deceased schizophrenic subjects (González-Maeso et al., 2008), and atypical antipsychotics block serotonin 5-HT2A receptors by as much as 90%
RESEARCH SPOTLIGHT
Antipsychotics and Their Side Effects

Antipsychotic medication is generally classified in two different categories: first-generation antipsychotics (FGA), and second-generation (atypical) drugs (SGA). Each has its own unique qualities and side effects. Although each is effective in preventing the positive symptoms of schizophrenia, they are less likely to affect the negative symptoms.

FGA drugs include Thorazine (chlorpromazine) and Haldol (haloperidol). Potent D₂ blockers, they help alleviate positive symptoms in most individuals with schizophrenia. They have four major categories of side effects (Preston, O’Neal, & Talaga, 2013). The first is called extrapyramidal effects and is a result of excessive blocking of dopamine receptors; impaired movement such as tardive dyskinesia, shuffling gait, tremors, and a blank facial expression are a result of damage to the basal ganglia (the “extrapyramidal” region) and mimic Parkinson’s disease. Although many of these side effects are immediately apparent with FGAs, the tardive dyskinesia is seen only after prolonged use. This is common for Haldol. Anticholinergic side effects are due to blocking acetylcholine receptors and the parasympathetic nervous system and includes dry mouth and eyes, constipation, and sedation; this is common for Thorazine. Antiadrenergic side effects are caused by blocking the sympathetic nervous system and can result in low blood pressure and lightheadedness.

SGA drugs include clozapine, Abilify (aripiprazole), Latuda (lurasidone), and Seroquel (quetiapine). They weakly block D₂ receptors but strongly block serotonin receptors. Because dopamine is not strongly blocked, there is a much smaller risk of extrapyramidal effects and tardive dyskinesia. However, these drugs carry their own set of undesirable side effects. They tend to cause sleepiness, can result in weight gain, and are more effective in reducing the negative symptoms of schizophrenia. Two major side effects that rarely occur are agranulocytosis (a life-threatening blood disorder; Ildänpään-Heikkilä, Alhava, Olkinuora, & Palva, 1977) and serotonin syndrome (which causes sweating, high body temperature, seizures, headaches, and confusion; Buckley, Dawson, & Isbister, 2014). Both are life threatening and must be treated by medical administration of either blood factors (for agranulocytosis) or serotonin agonists (for serotonin syndrome).

(H. M. Jones & Pilowsky, 2002; Kapur, Zipursky, & Remington, 1999). But serotonin has not received nearly as much attention as glutamate activity, which also is affected by atypical antipsychotics. The drug phencyclidine (PCP), which inhibits the NMDA (N-methyl-d-aspartic acid) subtype of glutamate receptor, mimics schizophrenia far better than amphetamine does, particularly in producing negative as well as positive symptoms (Sawa & Snyder, 2002). Glycine activates the NMDA receptor, and adding it or similar compounds to antipsychotic medications reduces both kinds of symptoms (Lisman et al., 2008). According to the glutamate theory, hypofunction of NMDA receptors results in increases in glutamate and downstream increases in dopamine, which together produce positive and negative symptoms of schizophrenia (Lisman et al.; Sendt, Giaroli, & Tracy, 2012). Indeed, genes that underlie glutamate signaling are correlated with the severity of schizophrenia and related disorders (N. L. O’Brien et al., 2014). However, it has been difficult to develop drugs that target NMDA receptors or reduce glutamate levels, and that are both therapeutically effective and well tolerated (Sendt et al.). Those that do work produce modest results, and a couple of them are in final phase 3 clinical trials.

Obviously, it would be a mistake to focus entirely on a single neurotransmitter, considering the complex interactions among them. The glutamate theory provides some recognition of this fact, and it is showing considerable usefulness in explaining schizophrenia and some promise in guiding drug development. While we wait for the glutamate story to unfold, we have additional clues about the origins of schizophrenia from structural and functional anomalies in the brain.

Brain Anomalies in Schizophrenia

Malfunctions have been identified in virtually every part of the brain in people with schizophrenia. The most consistent finding has been enlargement of the ventricles; another is hypofrontality, or reduced activity in the frontal lobes. We will examine each of these defects in turn.
Brain Tissue Deficits and Ventricular Enlargement

A signature characteristic of schizophrenia is a decrease in brain tissue, both gray and white matter, with deficits reported in at least 50 different brain areas (Honea, Crow, Passingham, & Mackay, 2005). The number of sites and the variability across studies attest to the multifaceted nature of schizophrenia, but the frequency with which deficiencies are found in the frontal and temporal lobes indicates that they are particularly important. These tissue losses are accompanied by alterations in neural functioning but not necessarily in the expected direction: Activity is decreased in the dorsolateral prefrontal cortex but increased in the orbitofrontal cortex and in a subregion of the hippocampus (Schobel et al., 2009). In fact, hippocampal activation is so characteristic of schizophrenia that in a group of people having brief psychotic symptoms, it identified with 70% accuracy those who would later be diagnosed with full-blown schizophrenia (Schobel et al.).

An indication of the tissue deficits seen in schizophrenia is ventricular enlargement; this is because the ventricles expand to take up space normally occupied by brain cells (Figure 14.8). Both deficiencies are usually subtle, on the order of less than a tablespoonful increase in ventricular volume (Suddath et al., 1989) and a 2% decrease in brain volume (Hajima et al., 2012; Harrison et al., 2003), but these figures belie the functional importance of the losses. In fact, an often-distinguishing feature between identical twins discordant for schizophrenia is the size of their ventricles (Suddath, Christison, Torrey, Casanova, & Weinberger, 1990). Ventricular enlargement is not specific to schizophrenia; enlarged ventricles are also associated with several other conditions, including old age, dementia (loss of cognitive abilities), Alzheimer’s disease, Huntington’s chorea (Weinberger & Wyatt, 1983), and alcoholism with dementia (D. M. Smith & Atkinson, 1995). Nor are enlarged ventricles an inherent characteristic of schizophrenia. As you can see in Figure 14.8a, several controls have enlarged ventricles, and many of the patients have ventricle sizes in the normal range. We will look more closely at the tissue deficits later when we consider their origins.

Hypofrontality

Earlier, we saw that prefrontal functioning can be assessed by using the gambling task; an alternative technique is the Wisconsin Card Sorting Test, which requires individuals to change strategies in midstream, first sorting cards using one criterion but then changing to another. Many people with schizophrenia perform poorly on the test, persisting with the previous sorting strategy. Normal individuals show increased activation in the prefrontal area during the test; schizophrenic patients typically do not, despite normal activation...
in other areas (D. R. Weinberger, Berman, & Zec, 1986). Figure 14.9 shows a normal brain practically light-
ing up during the test, in comparison with the schizophrenic brain, especially in the frontal area called the
dorsolateral prefrontal cortex. This hypofrontality apparently involves prefrontal dopamine deficiency; because
administering amphetamine increases blood flow in the prefrontal cortex and improves performance on
the Wisconsin Card Sorting Test (Daniel et al., 1991). Traumatic injury to the dorsolateral prefrontal cortex
causes impairments like the symptoms of schizophrenia: flat affect, social withdrawal, reduced intelligence
and problem-solving ability, diminished motivation and work capacity, and impaired attention and concen-
tration (Weinberger et al., 1986). Because of the frontal lobes’ involvement in planning actions, recognizing
the consequences of actions, and managing working memory, it is not surprising that frontal dysfunction
would cause major abnormalities in thinking and behavior.

Neural Connections and Synchrony
Recent attention has been shifting away from localized deficits and focusing instead on disrupted coordina-
tion of neural activity across brain areas. For example, in normal controls performing a working memory
task, activity in the hippocampal formation varies together with prefrontal activity, but this coordination
is absent in people with schizophrenia (Meyer-Lindberg et al., 2005). The hypofrontality seen during the
Wisconsin Card Sorting Test has been attributed to disrupted communication between the hippocam-
us and the prefrontal cortex (Weinberger, Berman, Suddath, & Torrey, 1992). Inadequate coordination
between brain areas is at least partly due to white matter reduction; white matter loss has been consistently
reported in the brains of people with schizophrenia, particularly in prefrontal and temporal areas (Begré &
Koenig, 2008; Ellison-Wright & Bullmore, 2009). Diffusion tensor imaging shows that the quality of con-
nections is compromised throughout much of the brain (B. R. Lee et al., 2013). Recent studies also docu-
mented an overall decrease in cortical thickness, changes in neuronal maturation, and reduced cortical
folding in the cingulate-frontal-temporal circuit, suggesting that hypofrontality may be a result of decreased
gray and white matter in frontal-associated circuits (Alexander-Bloch et al., 2014; Nanda et al., 2014).

![FIGURE 14.9 Blood Flow in Normal and Schizophrenic Brains During Card Sorting Test.](image)

(a) The upper images are of the left and right hemispheres of a normal brain; the schizophrenic brain is below. Red and yellow
represent greatest activation. Note especially the activity in the dorsolateral prefrontal cortex, whose location is identified in (b).

Source: (a) From “Physiologic Dysfunction of Dorsolateral Prefrontal Cortex in Schizophrenia: I. Regional Cerebral Blood Flow Evidence,” by D. R. Weinberger,
Reduced connectivity between frontal and posterior regions of the brain correlates with positive and negative symptoms as well as with performance on the Wisconsin Card Sorting Test.

Brain functioning is coordinated by synchronized firing that links the activity of neurons within a cortical area, across areas, and even between hemispheres. This synchronization is widely believed to be critical to perceptual binding and cognitive performance, and it is one of the functions disrupted in schizophrenia (Uhlhaas & Singer, 2010). Synchronized activity in frontal-thalamocortical circuits occurred at lower frequencies in patients (Ferrarelli et al., 2012), perhaps because the reduced white matter connections cannot support coordination at higher frequencies. Frequency reduction averaged 10 Hz in the frontal cortex; the deficit was greatest in the prefrontal area, and the frequency loss there was correlated with positive and negative symptoms. To some extent we can correlate the patterns of synchrony with the symptoms of schizophrenia; in patients with positive symptoms, for example, oscillation synchrony is enhanced within limited areas but is deficient between areas (Uhlhaas & Singer). This enhanced synchrony, which indicates hyperexcitability, is seen in the occipital area in visual hallucinators (Spencer et al., 2004) and in the left auditory cortex in auditory hallucinators (Spencer, Niznikiewicz, Nestor, Shenton, & McCarley, 2009). At the same time, auditory hallucinators fail to show normal synchrony between frontal and temporal areas while talking (Ford, Mathalon, Whitfield, Faustman, & Roth, 2002).

It may surprise you to learn that hallucinations are associated with activity in the respective sensory areas. Scans of the brains of people with schizophrenia show that language areas are active during auditory hallucinations and visual areas are active during visual hallucinations (Figure 14.10; McGuire, Shah, & Murray, 1993; McGuire et al., 1995; Silbersweig et al., 1995). Because these areas are activated in normal individuals when they are engaged in “inner speech” (talking to oneself) and imagining visual scenes, it appears that the hallucinating schizophrenic is not simply imagining voices and images but is misperceiving self-generated thoughts.

One of the most documented symptoms of schizophrenia is the inability to suppress environmental sounds. With sensory gating impaired, the intrusion of non-attended stimuli such as traffic noise or a distant conversation is not just annoying but can be interpreted by the person with schizophrenia as threatening. Impaired sensory gating can be a useful diagnostic tool for schizophrenia. Most people will “gate out” the second of two clicks presented a half-second apart, indicated by a reduction in the P50 EEG wave, but individuals with schizophrenia typically have an abnormal P50 wave (Figure 14.11). This deficit is also associated with reduced synchrony across wide areas of the brain (M. H. Hall, Taylor, Salisbury, & Levy, 2010). Atypical antipsychotics improve gating, but nicotine normalizes it (Adler et al., 2004; Kumari & Postma, 2005). The smoking rate declined in the United States from 42% in 1965 to about 15% in 2015 (Centers for Disease Control and Prevention, 2015b), but the rate remained about 80% among people with schizophrenia (Keltner & Grant, 2006), in an apparent attempt at self-medication. Besides sensory gating, nicotine improves several negative symptoms, including impaired visual tracking of moving objects, working memory, and other cognitive abilities (Sacco, Bannon, & George, 2004; Sacco et al., 2005; Tregellas, Tanabe, Martin, & Freedman, 2005). Nicotine appears to compensate for diminished functioning of nicotinic acetylcholine receptors (S. I. Deutsch et al., 2005), increase glutamate and GABA release, and increase dopamine levels in the prefrontal cortex where it is depleted in hypofrontality (Kumari & Postma; Sata et al., 2008). Three studies have linked schizophrenia with one of the genes responsible for nicotinic receptors (De Luca, Wang, et al., 2004; S. I. Deutsch et al., 2005).
There may very well be other changes to the brain due to schizophrenia. A large coalition of European researchers and pharmaceutical companies is undertaking a €16.5 million ($18.8 million) study called PRISM (Psychiatric Ratings Using Intermediate Stratified Markers); they will follow individuals with schizophrenia and other neurological disorders to determine the biological roots of the negative symptom of social withdrawal that is common to the groups (Underwood, 2016).

Environmental Origins of the Brain and Transmitter Anomalies

An obvious potential cause of brain defects would be head injury. Several studies have reported an association between schizophrenia and brain damage that occurred within a few years prior to diagnosis (reviewed in David & Prince, 2005). However, the studies have been criticized for several methodological inadequacies, including reliance on patients' and relatives' memory of the injuries, casual diagnosis of schizophrenia, and failure to consider accident proneness and preinjury symptoms as confounding factors (David & Prince, 2005; Nielsen, Mortensen, O'Callaghan, Mors, & Ewald, 2002). A later study of almost 114,000 Danish citizens found a correlation between severe head injury and schizophrenia; injury occurring between 11 and 14 years of age increased the likelihood of schizophrenia by 65% (Orlovska et al., 2014). However, researchers cannot separate the effects of the physical injury to the brain from the emotional effects of the stress and anxiety caused by the injury experience.

The evidence is stronger for a variety of influences at the time of birth or during the prenatal period. These include both physical complications (Cannon, Jones, & Murray, 2002) and emotional stresses on the mother, such as death of the father (Huttunen, 1989) and military invasion (van Os & Selten, 1998). Prenatal stress in mice results in upregulation of 5-HT2A receptors and downregulation of mGlu2 receptors, both of which are seen in the brains of schizophrenia patients (Holloway et al., 2013). One indication that birth and pregnancy complications contribute to brain deficits is that they are associated with enlarged ventricles later in life (Pearlson et al., 1989). They are a possible explanation for the difference in ventricle size between identical twins (Bracha, Torrey, Gottesman, Bigelow, & Cunniff, 1992).

It is easy to see how birth complications, such as being born with the umbilical cord around the neck, could differentiate between twins, but different experiences in the womb require some explanation. Identical twins may share the same placenta and amniotic sac or they may have their own, depending on whether the developing organism splits in two before or after the fourth day of development. Identical twins who did not share a placenta had an 11% concordance rate for schizophrenia, compared with 60% for those who shared a placenta, presumably due to the sharing of infections (J. O. Davis, Phelps, & Bracha, 1995). In spite of the importance of prenatal factors, some researchers believe that they produce schizophrenia only in individuals who are already genetically vulnerable (Schulsinger et al., 1984).

The winter birth effect refers to the fact that more people who develop schizophrenia are born during the winter and spring than during any other time of the year. The effect has been replicated in a large number of studies, some with more than 50,000 schizophrenic patients as subjects (T. N. Bradbury & Miller, 1985). The important factor in winter births is not cold weather, but the fact that infants born between January and May would have been in the second trimester of prenatal development in the fall or early winter, when there is a high incidence of infectious diseases (C. G. Watson, Kucala, Tilleskjar, & Jacobs, 1984). There is good evidence that the mother's exposure to viral infections during the fourth through sixth months of pregnancy (second trimester) increases the risk of schizophrenia. This appears to be caused not by the virus itself but by the immune reaction that it triggers. This conclusion is supported by a markedly higher level of interleukin-1β in the spinal fluid of first-episode patients, indicating that an immune response has occurred (Figure 14.12; Söderlund et al., 2009). Because the patients were infection free at the time, the infection must have occurred earlier, possibly during the prenatal period.

Several illnesses have been implicated, but the effect of influenza has been researched most frequently, and a higher incidence of schizophrenic births has been confirmed following influenza outbreaks in several countries.
Figure 14.13 shows that during years of high influenza infection the birth rate of people later diagnosed with schizophrenia increases during winter and spring; also, there is a peak of such births a few months after the start of epidemics. However, these studies could not confirm that the individual mothers had been exposed to the influenza virus; by analyzing the blood specimens drawn from expectant mothers, Alan Brown and his colleagues (2004) found a sevenfold increased risk for schizophrenia and spectrum disorders when influenza antibodies were present, and they estimated that influenza infection accounts for 14% of schizophrenia cases. As was the case with stress, maternal infection with the influenza virus upregulates 5-HT<sub>2A</sub> receptors and downregulates mGlu<sub>2</sub> receptors in the frontal cortex of the offspring (Moreno et al., 2011). Injecting pregnant mice with a drug that activates the immune system produced the same result, suggesting that immune responses are responsible for the receptor alterations in schizophrenia (Holloway et al., 2013).

Prenatal starvation is another pathway to schizophrenia that until recently was the subject of controversy. The idea came about after the rate of schizophrenia doubled among the offspring of mothers who were pregnant during Hitler’s 1944–1945 food blockade of the Netherlands (Susser et al., 1996). However, the interpretation was questionable because the sample was small and because toxins in the tulip bulbs the women ate to survive could have been to blame. But now data from a much larger sample of adults born during the 1959–1961 famine in China have confirmed the association, with an increase in schizophrenia from 0.84% to 2.15% (St. Clair et al., 2005).

Most of the environmental influences we have been discussing occur during pregnancy or birth; one, however, relates to the father. There is a greater risk of schizophrenia if the father’s age at the time of conception exceeds 25, and by paternal age of 50 the risk has increased by two thirds (B. Miller et al., 2010). The mechanism for this effect is unknown, but chances are it is epigenetic, due either to the normal aging process or to an accumulation of external environmental insults. Epigenetic effects in general can be traced to a variety of environmental influences, including toxins, diet, starvation, drugs, and stress; they likely account for most of the environmental influences we have been talking about. The fact that obesity in the Dutch hunger winter offspring was linked to epigenetic changes (see Chapter 6) makes us suspect the same mechanism in the cases of schizophrenia in that group. This is a relatively new area of investigation, so there has been little documentation of epigenetic influences in schizophrenia.

**Schizophrenia as a Developmental Disease**

The defects in the brains of people diagnosed with schizophrenia apparently occur early in life, some at the time of birth or before. In some cases, it appears that many neurons in the temporal and frontal lobes failed to migrate to the outer areas of the cortex during the second trimester; they are disorganized and mislocated in
Part IV: Complex Behavior


The neurons in the normal hippocampus have an orderly arrangement (a), but in the brain of an individual with schizophrenia you can see that they have migrated in a haphazard fashion (b).

Source: © Arne Scheibel, UCLA.

the deeper white layers (Figure 14.14; Akbarian, Bunney, et al., 1993; Akbarian, Viñuela, et al., 1993). The hippocampus and prefrontal cortex are 30%–50% deficient in reelin, a protein that functions as a stop factor for migrating neurons (Fatemi, Earle, & McMenomy, 2000; Guidotti et al., 2000). In addition, neurons generated from stem cells derived from skin cells of individuals with schizophrenia exhibited impairment of signaling molecules that are responsible for neuronal differentiation (Topol et al., 2016). These observations and the association of schizophrenia with birth trauma and prenatal viral infection all argue for early damage to the brain or a disruption of development.

This view is supported by behavioral data. Home movies of children who later became schizophrenic revealed more negative facial expressions and physical awkwardness than in their healthy siblings; the movies were rated by judges who were unaware of the children's later outcome (Walker, Lewine, & Neumann, 1996). Among New Zealanders followed from age 3 to 32, those who later developed schizophrenia had deficits in learning, attention, and problem solving during childhood, and for each year of life they fell an additional two to three months further behind other children (Reichenberg et al., 2010).

Gray matter deficit and ventricular enlargement are ordinarily present at the time of patients' diagnosis (Degreaf et al., 1992). Most of the evidence indicates that the loss of brain volume occurs rapidly and dramatically in adolescence or young adulthood and then levels off (B. T. Woods, 1998). Adolescence is a particularly significant period in the development of schizophrenia. This is a time when symptoms of schizophrenia often begin to develop and a time of brain maturation, including frontal myelination and connection of temporal limbic areas (D. R. Weinberger & Lipska, 1995). Thompson, Vidal, et al. (2001) identified a group of adolescents who had been diagnosed with schizophrenia and used MRIs to track their brain development. At the age of 13, there was little departure from the normal amount of gray matter loss that occurs with circuit pruning, but over the next five years, loss occurred in some areas as rapidly as 5% per year (Figure 14.15). The nature of the symptoms varied as the loss progressed from parietal to temporal to frontal areas. Studies have found no evidence of dying neurons or of...
the inflammation that would be expected with an ongoing degenerative disease; instead, gray matter deficits have been attributed to loss of synapses (Jarskog, Glantz, Gilmore, & Lieberman, 2005; D. A. Lewis & Levitt, 2002; D. R. Weinberger, 1987). This apparent severe pruning may reflect the elimination of circuits that have already been diminished (D. A. Lewis & Levitt) by a lack of glutamate activity (Coyle, 2006) or through neuronal cell death pathways (Jarskog et al., 2005); this view is supported by the fact that the diagnosis of schizophrenia preceded significant gray matter reductions in the schizophrenic adolescents.

CONCEPT CHECK
Take a Minute to Check Your Knowledge and Understanding

- What is the interplay between heredity and environment in schizophrenia?
- Describe the two symptom categories of schizophrenia.
- How are dopamine irregularities and brain deficits proposed to interact?
- What role does glutamate play in schizophrenia?

Affective Disorders

The affective (mood) disorders include depressive disorders, mania, and bipolar disorders (Figure 14.16). Almost all of us occasionally experience depression, an intense feeling of sadness; we feel depressed over grades, a bad relationship, or loss of a loved one. This reactive depression can be severe, but major depression goes beyond the normal reaction to life’s challenges. In a major (or unipolar) depressive disorder (MDD), a person often feels sad to the point of hopelessness for weeks at a time; loses the ability to enjoy life, relationships, and sex; and experiences loss of energy and appetite, slowness of thought, and sleep disturbance. In some cases, the person is also agitated or restless. Stress is often a contributing factor, but major depression can occur for no apparent reason. Mania involves excess energy and confidence that often lead to grandiose schemes; decreased need for sleep, increased sexual drive, and abuse of drugs are common.

The DSM-5 now considers bipolar disorder to be a cluster of disorders, separate from depressive disorders and serving as a bridge between depression and schizophrenia (American Psychiatric Association, 2013). Bipolar disorder was once called “manic-depressive” disorder, but as you will learn in this chapter, mania is not always a characteristic of this group of disorders. In bipolar disorder, a person alternates between periods of depression and either mania (bipolar I) or hypomania (bipolar II); mania can occur in the absence of depression, but this is rare and the treatment is the same as for bipolar I disorder. In addition, bipolar I patients often demonstrate psychotic features such as delusions, hallucinations, paranoia, or bizarre behavior, which has led psychologists to consider bipolar I as a bridge disorder between schizophrenia and depression. Finally, there is a third major category of bipolar disorder called cyclothymic disorder, in which individuals cycle rapidly between hypomania and mild depression. Two quotes provide some insight into the disorders from the patients’ own perspectives (National Institute of Mental Health, 1986):

Depression: I doubt completely my ability to do anything well. It seems as though my mind has slowed down and burned out to the point of being virtually useless. . . . I am haunted . . . with the total, the desperate hopelessness of it all. . . . If I can’t feel, move, think, or care, then what on earth is the point?

Mania: At first when I’m high, it’s tremendous . . . ideas are fast . . . like shooting stars you follow until brighter ones appear . . . all shyness disappears, the right words and gestures are suddenly there. . . . Sensuality is pervasive, the desire to seduce and be seduced is irresistible. Your marrow is infused with unbelievable feelings of ease, power, well-being, omnipotence, euphoria . . . you can do anything . . . but, somewhere this changes.
The most recent data indicate that 3 out of 10 people will suffer a mood disorder in their lifetimes, most likely depression (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). Women are two to three times more likely than men to suffer from MDD during their lifetimes; bipolar disorder occurs equally often in both sexes (Gershon, Bunney, Leckman, Van Eerdewegh, & DeBauche, 1976; P. W. Gold, Goodwin, & Chrousos, 1988) at a rate of about 4.5% (Kessler, Merikangas, & Wang, 2007). The risk for MDD increases with age in men, whereas women experience their peak risk between the ages of 35 and 45; the period of greatest risk for bipolar disorder is in the early 20s to around the age of 30. Getting a handle on the economic burden of these disorders is difficult, because it depends on what costs are included and what assumptions are made. Estimates of the annual cost for all mood disorders in the United States have varied from $24 billion to $234 billion (Dilsaver, 2011; Greenberg et al., 2003; Uhl & Grow, 2004). Regardless of the economic cost, by 2020 depression will be the second largest cause of disability worldwide (Patel, 2009).

**Heredity**

As with schizophrenia, there is strong evidence that affective disorders are partially heritable. Part of that evidence is the increased incidence of affective disorders among patients’ relatives. When one identical twin has an affective disorder, the probability that the other twin will have the illness as well is about 69%, compared with 13% in fraternal twins (Gershon et al., 1976). Lack of complete concordance in identical twins indicates that there is an environmental contribution. However, the concordance rate drops surprisingly little when identical twins are reared apart (J. Price, 1968), which may mean that the most important environmental influences occur in the prenatal period or shortly after.

Genetic liability differs by gender; a Swedish twin study estimated heritability at 29% for men and 42% for women (Kendler, Gatz, Gardner, & Pedersen, 2006). These results were consistent with studies in the United States and Australia, as well as with studies that identified different chromosomal locations for risk factors in men and women. In one study, seven genes were exclusive to men, nine were exclusive to women, and only three were shared between men and women (Zubenko, Hughes, Staffler, Zubenko, & Kaplan, 2002). The sex disparity suggests one reason disorder genes can be difficult to locate in a clinical group, and it may explain the higher frequency of depression in women and the higher rate of suicide in men.

Once again, the genes we are interested in are many and of small effect, requiring much larger sample sizes than are typically employed. Researchers are more and more resorting to meta-analyses, which pool the results of many studies. One finding is that the 5-HTTLPR portion of the SLC6A4 serotonin transporter gene has been associated with an increased vulnerability to depression, along with a 15% reduction in gray matter in the amygdala and a 25% reduction in the subgenual anterior cingulate cortex (Pezawas et al., 2005). People with the short variation show an exaggerated amygdala response to fearful facial expressions (Hariri et al., 2002), apparently due to a loss of feedback from the cingulate cortex that would ordinarily dampen amygdala activity (Pezawas et al., 2005). According to some studies, these deficiencies increase susceptibility to stress, which leads to depression (Figure 14.17; Canli et al., 2006; Caspi et al., 2003). Although a meta-analysis that pooled 56 studies produced a strong confirmation of the linkage (Karg, Burmeister, Shedden, & Sen, 2011), not all studies have confirmed it. One reason may be that studies rarely consider gene interactions such as epistasis, the suppression of one gene’s effect by another. In this case, the VAL66MET allele of the gene for brain-derived neurotrophic factor (BDNF), a protein that encourages neuron growth and survival, protects against the effects of the 5-HTTLPR short allele on brain development (Pezawas et al., 2008). A later meta-analysis confirmed that VAL66MET also reduces vulnerability to depression (Hosang, Shiles, Tansey, McGuffin, & Uher, 2014).

Whole-genome studies have been extremely beneficial because researchers can explore the genome without any hypothesis or even an educated guess about what to look for. But the statistical procedure used to confirm an association must be corrected for the increased probability of a chance “hit” due to the millions of comparisons performed, which makes it even harder to find genes that have a small effect. One solution is to increase the effect size by targeting a limited group of subjects; a gene location on chromosome 3 was identified only when researchers limited their search to patients with severe depression (Breen et al., 2011). Another approach is to limit the search to the genes known to be involved in a relevant pathway; knowledge that the immune system is dysregulated in depression led researchers to discover several candidate immune system genes (Bufalino, Hepgui, Aguglia, & Pariaante, 2013).

A common characteristic of depression is disruption of the circadian (day–night) cycle, which is controlled by numerous genes (Bunney et al., 2015). At last count, at least 11 circadian genes were disrupted in patients with
major depression (J. Z. Li et al., 2013). These genes are in the pineal gland (which secretes the sleep-inducing hormone melatonin), the pituitary gland (which controls hormone levels in the body), and most important, the anterior cingulate cortex (which, as we discussed in Chapter 8, is involved in autonomic functions, reward, decision making, and emotion). It is this last area that probably causes the alteration in mood we see in affective disorders.

Despite similarities between depression and bipolar disorder, they are genetically independent of each other (P. W. Gold et al., 1988; Moldin, Reich, & Rice, 1991). In fact, there is a much higher genetic correlation between bipolar disorder and schizophrenia (68%) than mood disorders (43%; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Bipolar disorder is more heritable than either depression or schizophrenia, with estimates of 85% and 93% (Kiesewetter, Partonen, Haukka, Kaprio, & Lönnqvist, 2004; McGuffin et al., 2003). Few genes have been confirmed, however, apparently again because of small sample sizes. An unusually large genome-wide study that included 9,747 patients confirmed three previously discovered genes and added two more (Mühleisen et al., 2014). The genes' functions involve a calcium channel at the nodes of Ranvier and cellular functioning and signaling. The Cross-Disorder Group study, with 33,332 patients, reported that some genes are shared among five disorders: bipolar disorder, major depressive disorder, schizophrenia, autism spectrum disorders, and attention-deficit/hyperactivity disorder (Cross-Disorder Group of the Psychiatric Genomics Consortium). Genetic sharing is one of the arguments for considering these disorders as a continuum. Whether that is appropriate or not, you should understand that all five of these disorders do have a variety of functional and structural characteristics in common. Finally, mutations have been found in bipolar patients in three genes that control circadian rhythms, none of which overlapped with the five associated with depression (McGrath et al., 2009; Soria et al., 2010).

### The Monoamine Hypothesis of Depression

The first effective treatment for depression was discovered accidentally, and theory again followed practice rather than the other way around. Iproniazid was introduced as a treatment for tuberculosis, but it was soon discovered that the drug produced elevation of mood (Crane, 1957) and was an effective antidepressant (Schildkraut, 1965). Iproniazid was later abandoned as an antidepressant because of its side effects, but its ability to increase activity at the monoamine receptors led researchers to the monoamine hypothesis, that depression involves reduced activity at norepinephrine and serotonin synapses. You may remember that the

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**FIGURE 14.17 The Role of Stress and the Serotonin Transporter Gene in Depression.**

(a) In individuals with either one or two copies of the so-called short allele, the percentage who were diagnosed at age 26 with depression increased with the number of stressful life events in the past five years. (b) In those with two copies of the long allele, the number of stressful events made no difference. Life events were assessed from a checklist of 14 employment, financial, housing, health, and relationship stressors.

monoamines also include dopamine, but because dopamine agonists such as amphetamines produced inconsistent therapeutic results, researchers have limited their interest to norepinephrine and serotonin.

All the effective antidepressant drugs increase the activity of norepinephrine or serotonin, or both, at the synapses. They do this in different ways. Some block the destruction of excess monoamines by enzymes in the terminals (monoamine oxidase inhibitors), whereas others block reuptake at the synapse (tricyclic antidepressants). Atypical (second-generation) antidepressants affect a single neurotransmitter; for example, Prozac (fluoxetine) is one of several selective serotonin reuptake inhibitors. Finally, some antidepressants have a mixed effect on multiple neurotransmitter systems and are effective for specific combinations of disorders. For instance, Cymbalta (duloxetine) is one of several serotonin and norepinephrine reuptake inhibitors. This last group's effectiveness truly supports the monoamine hypothesis. The synaptic effects of antidepressants can occur within hours, but symptom improvement usually takes two to three weeks through the gradual modification of cortical circuits.

Additional evidence to support the monoamine hypothesis is that serotonin and norepinephrine are involved in behaviors that are disturbed in affective disorders. Serotonin plays a role in mood, activity level, sleep and daily rhythms, feeding behavior, sexual activity, body temperature regulation, and cognitive function (Meltzer, 1990; Siever et al., 1991). Because the noradrenergic system is involved in responsiveness and sensitivity to the environment, reduced norepinephrine activity may contribute to the depressed individual's slowed behavior, lack of goal-directed activity, and unresponsiveness to environmental change (Siever et al.).

Earlier, we saw that nicotine provides some relief from symptoms of schizophrenia. Nonnicotine ingredients in tobacco smoke also have been found to act as monoamine oxidase inhibitors. This would explain why smoking is so frequent among those with depression and why they have difficulty giving up smoking (J. S. Fowler et al., 1996; Khalil, Davies, & Catagnoli, 2006). We mention a therapeutic effect of smoking for the second time only to illustrate again how people may self-medicate without being aware they are doing it and why some people have so much trouble quitting; if it sounds as though the benefits of smoking outweigh the cost to the smoker's health, reread the section on nicotine in Chapter 5.

Figure 14.18 is a dramatic demonstration of the extensive effect of smoking on monoamine oxidase inhibitor levels throughout the body.

Treatment resistance and the delay required for drugs to take effect are serious issues, especially if the patient is suicidal. Experiments with ketamine, which was developed as an anesthetic but gained infamy as a club drug, suggest that these problems might be avoidable. In a study with patients who had shown resistance to at least two antidepressant drugs, a single injection of ketamine alleviated depression in 68%, and the improvement lasted seven days in 46% of the patients (Murrough et al., 2013). Relapse time is highly variable, though, and ketamine appears to be most valuable as a temporary treatment (aan het Rot et al., 2010). Ketamine also interests us because its effect is not on norepinephrine or serotonin; instead, it has its antidepressant effect by activating AMPA receptors (Zanos et al., 2016), implicating glutamate function in depression as well as in schizophrenia.

About 30%–50% of depressed patients fail to respond to drug therapy; a statistic made worse by the fact that the placebo response rate alone is 30% (Depression Guideline Panel, 1993). Lack of response is
partly related to symptom severity; patients with mild or moderate symptoms receive little or no relief, but for patients with severe depression the benefit of medications is substantial (Fournier et al., 2010). So how do we treat drug-resistant forms of depression? Cognitive-behavioral therapy is generally about as effective as antidepressants, and when it was added to the usual treatment in resistant patients, depression scores improved by 50% or more in 46% of patients, compared with 22% in those who remained in typical treatment (Wiles et al., 2013). One thing that must be clear to you by now is how much therapeutic effectiveness depends on designing drugs to affect the right receptors and avoiding effects at sites that would produce side effects. This is the subject of the accompanying Application.

APPLICATION
Targeting Drugs to Specific Receptors

As we have already mentioned, the most prescribed class of antidepressant medications today is the selective serotonin reuptake inhibitors (SSRIs). Although mood disorders are most commonly linked to serotonin (5-HT), abnormal function of other receptors and neurotransmitters can cause similar behavioral changes. For instance, there could be an imbalance of norepinephrine or dopamine. Newer antidepressant medications are designed to stimulate different classes of receptors or to bind to only one of several receptor subtypes. For instance, a class of drugs called SNRIs increases the amounts of both serotonin and norepinephrine, which is useful for individuals with depression as well as emotional pain. Examples of these drugs include Cymbalta, Effexor, and Pristiq. Another class is the NDRIs, a relatively new class of drugs that raise norepinephrine as well as dopamine levels. These drugs are useful for treating some types of depression as well as attention-deficit/hyperactivity disorder (ADHD). Examples of this group include Focalin, Ritalin, Concerta, and Wellbutrin. One drug that targets a specific receptor subtype is the atypical antipsychotic Pimavanserin (in clinical trials), which specifically treats psychosis associated with Parkinson’s disease by stimulating 5-HT2A receptors and leaving the other serotonin receptor subtypes alone (Friedman, 2013). Another drug, Cariprazine, stimulates the D2 receptor family and not the D1 subfamily, which improves mania symptoms of both schizophrenia and bipolar I (Tohen, 2015). One of the oddest atypical antidepressants is Remeron (mirtazapine), which is classified as a norepinephrine and specific serotonergic antidepressant (NaSSA). This drug enhances the release of norepinephrine, increases serotonin release by presynaptic neurons, and modulates serotonin receptors in a complex way: it blocks 5-HT2 and 5-HT3 receptors so that the increased serotonin can bind only to 5-HT1 receptors (Antilla & Leinonen, 2001). The 5-HT2 and 5-HT3 receptors are associated with anxiety, changes in appetite, sexual dysfunction, and memory problems, so targeting only the 5-HT1 receptors provides effective antidepressant relief without as many side effects as with SSRIs (Schreiber, Melon, & DeVry, 1998).

As we just indicated, there are many types of each receptor in your nervous system. You have at least seven different serotonin receptor families, two dopamine receptor families, and at least five norepinephrine receptors (two alpha and three beta). Many of these receptors are found not only in the brain but also throughout the body, and stimulating them broadly using tricyclic antidepressants, MAOIs, or even SSRIs triggers most of the unpleasant side effects of those drugs. The future of psychopharmacology will therefore be in designer drugs that interact only with a subset of receptors that match an individual’s symptoms and neurobiology.
Electroconvulsive Therapy

In extreme cases of treatment nonresponse or because of suicidal behaviors, an alternative is electroconvulsive therapy. Electroconvulsive therapy (ECT) involves applying 70–130 volts of electricity to the head of an anesthetized patient, which produces a seizure accompanied by convulsive contractions of the neck and limbs and lasting about a half minute to a minute (Figure 14.19). Without the seizure activity in the brain that produces the convulsions, the treatment does not work. Within a few minutes, the patient is conscious and coherent, though perhaps a bit confused; the patient does not remember the experience. Usually ECT is administered two to three times a week for a total of 6–12 treatments.

ECT is the most controversial of the psychiatric therapies. Producing convulsions by sending a jolt of electricity through the brain sounds inhumane, and in fact the procedures used in the early days of ECT treatment often resulted in bone fractures and long-term memory deficits. Now patients are anesthetized and given muscle relaxants that eliminate injury and reduce emotional stress. The numbers of treatments and the voltage have been reduced, and stimulation is delivered in brief pulses rather than continuously. Though bilateral electrode placement produces a faster response that is desirable with suicidal patients, unilateral right hemisphere placement is usually favored because it minimizes cognitive side effects, such as temporary memory impairment (Kellner, Tobias, & Wiegand, 2010). These changes have made ECT safer and more effective (Weiner & Krystal, 1994). Follow-up studies indicate that memory and cognitive impairment induced by ECT dissipates within a few months (Crowe, 1984; Weeks, Freeman, & Kendell, 1980) and that cognitive performance even improves over pretreatment levels as the depression lifts (Sackeim et al., 1993). Brain scans and autopsies of patients and actual cell counts in animal subjects show no evidence of brain damage following ECT (reviewed in Devanand, Dwork, Hutchinson, Bolwig, & Sackheim, 1994).

ECT is usually reserved for patients who do not respond to the medications or who cannot take them due to extreme side effects or because of pregnancy. In a recent analysis of 13 studies that compared ECT with antidepressant drugs, 79% of patients responded to ECT, compared with 54% of patients treated with antidepressants (Pagnin, de Queiroz, Pini, & Cassano, 2004). ECT works especially well when depression or mania is accompanied by psychosis (Depression Guideline Panel, 1993; Potter & Rudorfer, 1993), and it works rapidly, which is beneficial to suicidal patients who cannot wait for weeks while a drug takes effect (Rudorfer, Henry, & Sackeim, 1997). The disadvantage of ECT is that it is often short term, but the patient can usually be maintained on drug therapy once a round of ECT has been completed.

ECT is effective with depression, mania, and schizophrenia, which suggests that its effects are complex, and research bears this out. Several changes occur at the brain's synapses. Like the drugs, ECT increases the sensitivity of postsynaptic serotonin receptors (Mann, Arango, & Underwood, 1990); in addition, the sensitivity of autoreceptors on the terminals of norepinephrine- and dopamine-releasing neurons is reduced, so the release of those transmitters is increased. A temporary slowing of the EEG, which is correlated with therapeutic effectiveness, suggests that ECT synchronizes neuronal firing over large areas of the brain (Ishihara & Sasa, 1999; Sackeim et al., 1996). This reduced excitability is likely due to the fact that ECT increases diminished GABA concentrations (Sanacora et al., 2003). However, as you will see in the next section, both antidepressants and ECT now appear to trigger dramatic remodeling of the depressed brain.

Antidepressants, ECT, and Neural Plasticity

Although antidepressant drugs and ECT have been used to treat depression for more than half a century, we are not sure how they work. Most puzzling is the delay between neurotransmitter changes and symptom relief; hypotheses that changes in receptor sensitivity account for the delay have not been successful (Yamada, Yamada, & Higuchi, 2005). A promising lead is that antidepressant drugs, lithium, and ECT all increase neuronal birth rate in the hippocampus, at least in rodents and presumably in humans as well (Figure 14.20;
Inta et al., 2013; Mendez-David, Hen, Gardier, & David, 2013; Sairanen, Lucas, Ernfors, Castrén, & Castrén, 2005). Although increased neurogenesis can be detected within hours of antidepressant treatment, the time required for new hippocampal neurons to migrate to their new locations and form functional connections closely matches the delay in symptom improvement (Sairanen et al., 2005).

After new cell development was blocked by X radiation, antidepressants no longer had an effect in mice, suggesting that neurogenesis is required for antidepressant action (Santarelli et al., 2003). An increase in cell numbers is not the basis, however, because cell death also accelerates; some researchers have suggested that the therapeutic effect is due to the greater plasticity of new cells (Gould & Gross, 2002), a point we saw in Chapter 12 in relation to their lower threshold for LTP. However, when researchers used a drug instead of X radiation to block neurogenesis, antidepressant effect was not diminished (Bessa et al., 2009). All three of the antidepressant drugs used increased dendritic remodeling and synaptic contact; this led the researchers to conclude that antidepressant drugs work by enhancing plasticity rather than by promoting neurogenesis. There is additional evidence for a plasticity hypothesis: Both antidepressants and ECT modify activity in a large number of genes, especially in the hippocampus; most of those genes contribute to neural plasticity and neuron survival, as well as to neurogenesis (Altar et al., 2004; Yamada et al., 2005). Neurogenesis might contribute to antidepressant effect, but it appears that restoration of plasticity is more important.

### Rhythms and Affective Disorders

As we mentioned earlier, several circadian rhythm genes are implicated in depression, so it should be no surprise that depressed people often have problems with their biological rhythms. The circadian rhythm—the one that is a day in length—tends to be phase advanced in patients with affective disorders; this means that the person feels sleepy early in the evening and then wakes up in the early morning hours, regardless of the previous evening’s bedtime (Dew et al., 1996). The person also enters rapid eye movement sleep earlier in the night and spends more time in this state than normal (Kupfer, 1976). As you will learn in Chapter 15, rapid eye movement (REM) sleep is the stage of sleep during which dreaming occurs; the excess REM sleep is at the expense of the other stages of sleep. Patients with unipolar depression share this early onset of REM sleep with 70% of their relatives, and relatives with reduced REM latency are three times more likely to be depressed than relatives without reduced latency (Giles, Biggs, Rush, & Roffwarg, 1988).

#### Circadian Rhythms and Antidepressant Therapy

Some patients who are unresponsive to antidepressant medication can get relief from their depression by readjusting their circadian rhythm. They can do this simply by staying up a half hour later each night until...
they reach the desired bedtime. In some patients, this treatment results in a relief from depression that lasts for months (D. A. Sack, Nurnberger, Rosenthal, Ashburn, & Wehr, 1985).

Some depressed patients also benefit temporarily from sleep deprivation. This was initially seen with REM sleep deprivation, which is accomplished by waking the person every time the EEG indicates that sleep has moved into the REM stage (J. C. Wu & Bunney, 1990). Interestingly, most antidepressant drugs also suppress REM sleep (G. W. Vogel, Buffenstein, Minter, & Hennessey, 1990). Later research showed that depressed individuals also improve following non-REM sleep deprivation (Landsness, Goldstein, Peterson, Tononi, & Benca, 2011) or total overnight sleep deprivation (Giedke & Schwärzler, 2002). To find out why, researchers at Tufts University School of Medicine dosed mice with a drug that mimics adenosine, a compound that builds up in the brain during wakefulness and produces sleepiness. Twelve hours later the mice showed increased resistance to treatments that produce depressive-like behavior (Hines, Schmitt, Hines, Moss, & Haydon, 2013). The mice slept normally, perhaps because the drug targeted only the A1 type of adenosine receptor; a similar drug might provide humans the antidepressant benefits of sleep deprivation without the sleepiness.

**Seasonal Affective Disorder**

There is another rhythm that is important in affective disorders; some people’s depression rises and falls with the seasons and is known as seasonal affective disorder (SAD). This is on a circannual rhythm, or one that follows the changes of the seasons. Most SAD patients are more depressed during the fall and winter, and then improve in the spring and summer, which parallels onset for schizophrenia as well (Owens & McGorry, 2003). Others are more depressed in the summer and feel better during the winter. Members of either group may experience a mild mania-like activation called hypomania during their “good” season. While depressed, they usually sleep excessively, and they often have increased appetites, especially for carbohydrates, and gain weight. The length of day and the amount of natural light appear to be important in winter depression; symptoms improve when the patient travels farther south (or north, if the person lives in the Southern Hemisphere) even for a few days, and some report increased depression during cloudy periods in the summer or when they move to an office with fewer windows. Summer depression appears to be temperature related: Traveling to a cooler climate, spending time in an air-conditioned house, and taking several cold showers a day improves the symptoms. About 10% of all cases of affective disorder are seasonal, and 71% of SAD patients are women (Faedda et al., 1993). Although seasonal influences on affective disorder have been known for 2,000 years and documented since the mid-1850s, summer depression has received relatively little attention, so we will restrict our discussion to winter depression.

A treatment for winter depression is phototherapy—having the patient sit in front of high-intensity lights for a couple of hours or more a day (Figure 14.21). Patients begin to respond after two to four days of treatment with light that approximates sunlight from a window on a clear spring day; they relapse in about the same amount of time following withdrawal of treatment (Rosenthal et al., 1985). The fact that midday phototherapy is effective suggests that the increased amount of light is more important than extending the length of the shortened winter day; the observation that suicide rate is related to a locale’s amount of clear sunlight rather than the number of hours of daylight supports this conclusion (Wehr et al., 1986). Phototherapy resets the circadian rhythm (Lewy, Sack, Miller, & Hoban, 1987), so it is also helpful with circadian rhythm problems including jet lag, delayed sleep syndrome, and difficulties associated with shift work (Blehar & Rosenthal, 1989).

Physiological mechanisms for disorders of circadian and circannual rhythms include both neurotransmitter and prefrontal cortex changes. Lowered serotonin activity is involved in winter depression. Drugs that increase serotonin activity alleviate the depression and reduce carbohydrate craving (O’Rourke, Wurtman, Wurtman, Chebli, & Gleason, 1989). As we saw in Chapter 5, eating carbohydrates increases brain serotonin levels. So, rather than thinking that SAD patients lack willpower when they binge on junk food and gain weight, it might be more accurate to think of them as self-medicating with carbohydrates. But what areas of the brain change seasonally? A recent study suggests that the dorsolateral prefrontal cortex contains genes activated on a seasonal basis (Lim et al., 2017).
Bipolar Disorder and Related Disorders

The mystery of major depression is far from solved, but bipolar disorder is even more puzzling. Bipolar patients vary greatly in their symptoms: The depressive cycle usually lasts longer than mania, but either may predomi-
nate. There are three major forms of bipolar disorder: bipolar I (major depressive episodes with occasional mania
cycles), bipolar II (major depression with mild hypomanic episodes), and cyclothymic disorder (frequent alternation
between hypomanic and mild depressive episodes that are not severe enough for a diagnosis of bipolar II).
Some patients cycle between depression and mania regularly (this is called rapid cycling), whereas others are
unpredictable; cycles usually vary from weeks to months in duration, although some patients switch as frequently
as every 48 hours (Bunney, Murphy, Goodwin, & Borge, 1972). Stress often precipitates the transition from
depression into mania, followed by a more spontaneous change back to depression; the prospect of discharge
from the hospital is particularly stressful and often will precipitate the switch into mania. However, as bipolar
disorder progresses, manic episodes tend to occur independently of life's stresses (P. W. Gold et al., 1988).

It appears that bipolar disorder involves increased sensitivity to dopamine and either decreased sensitivity to
serotonin or a more general dysregulation in the dopaminergic system (Miklowitz & Johnson, 2006). Drugs used
to treat the disorder include several atypical antipsychotics, as well as carbamazepine, valproate, and lithium.
Carbamazepine and valproate stabilize electrical activity in the brain and are typically used as anticonvulsants
for the treatment of epilepsy. Lithium, a metal administered in the form of lithium carbonate, is the medication
of choice for bipolar illness; it is most effective during the manic phase, but it also prevents further depressive
episodes. Examination of lithium's effects has not identified any critical neurotransmitters; partly because lithium
affects several transmitter systems (Worley, Heller, Snyder, & Baraban, 1988). It may be that lithium stabilizes
neurotransmitter and receptor systems to prevent the large swings seen in manic-depressive cycling; its dual
role as an antidepressant argues for a normalizing effect rather than a directional one (Gitlin & Altshuler, 1997).
Closer examination, however, has revealed a specific effect on mania; lithium and valproate indirectly inhibit
protein kinase C (PKC), a family of intracellular messengers that regulate neural excitability. The breast cancer
drug tamoxifen is used to block estrogen receptors, but it also inhibits PKC. In a phase 2 clinical trial, 90% of
patients receiving tamoxifen with lithium were considered in remission, versus 55% receiving lithium alone
(Amrallahi et al., 2011). Tamoxifen itself may not be practical as a treatment for bipolar disorder because it antagonizes
estrogen activity; if the drug continues to prove effective, an alternative that targets PKC only will have to be found.

Brain Anomalies in Affective Disorders

As with schizophrenia, affective disorders are associated with structural abnormalities in several brain areas.
Again, a larger ventricle size suggests loss of brain tissue, but the reductions are small and are not always found
(Depeu & Iacono, 1989). A review of numerous studies of depression reveals volume deficits in prefrontal areas,
especially the dorsolateral cortex and the anterior cingulate cortex as well as in the hippocampus, but an
increased volume in the amygdala (R. J. Davidson, Pizzagalli, Nitschke, & Putnam, 2002). Volume reduction apparently
precedes depression rather than being a degenerative consequence of it; it is evident at the time of patients' first
episode, and it can even be detected in the nondepressed offspring of patients (M. C. Chen, Hamilton, & Gotlib, 2010;
Peterson et al., 2009; Zou et al., 2010).

These structural alterations are accompanied by changes in activity level. Not surprisingly, total brain activity is reduced in unipolar patients (Sackeim et al., 1990) and in bipolar patients when they are depressed (Baxter et al., 1989). Gray matter is particularly reduced in the hippocampus, the orbitofrontal cortex that regulates emotions (Figure 14.22; Egger et al., 2008),

FIGURE 14.22 Reduction in Gray Matter in Elderly Depressed Patients.

Elderly patients with depression exhibited significant declines in gray matter in the amygdala (a), orbitofrontal
cortex (b), and hippocampus (b, c). Yellow indicates severity of loss compared to elderly patients without depression.

Source: (a) From “A Functional Anatomical Study of Unipolar Depression,” by W. C. Drevets et al., Journal of Neuroscience, 12,
pp. 3628–3641, © 1992 Society for Neuroscience. Used with permission. (b) From “Reduction of Prefrontal Cortex Glucose
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basal forebrain (Ribiez et al., 2013), prefrontal cortex, and cingulate cortex (Arnone, McIntosh, Ebmeier, Munafò, & Anderson, 2012). These decreases in brain tissue volume have been postulated to be predictors not only for depression but also for the likelihood that the person will improve following antidepressant treatment (Ribiez et al.). What is surprising is that some areas are more active in depressed patients. In unipolar depression, blood flow is higher in the amygdala and a frontal area connected to the amygdala called the ventral prefrontal cortex (Figure 14.23). The ventral prefrontal area may also be a “depression switch,” because activation comes and goes with bouts of depression. The amygdala continues to be active between episodes and returns to normal only after the remission of symptoms. Activity in the amygdala corresponds to the trait of depression—the continuing disorder—whereas activation of the ventral prefrontal area indicates the state of depression, which subsides from time to time in some individuals (Drevets, 2001; Drevets et al., 1992; Drevets & Raichle, 1995).

It is also not surprising that during a manic episode, brain metabolism increases from its depressed level by 4%–36% (Figure 14.24; Baxter et al., 1989). The subgenual prefrontal cortex is particularly interesting because it has been suggested as a possible “switch” controlling bipolar cycling (Figure 14.25). Its metabolic activity is reduced during both unipolar and bipolar depression, but increases during manic episodes (Drevets et al., 1997). The structure is a part of the cingulate cortex, located at the midline; it is in a good position to act as a bipolar switch, because it has extensive connections to emotion centers such as the amygdala and the lateral hypothalamus and it helps regulate neurotransmitters involved in affective disorders. Imaging studies also implicate the anterior parts of the limbic system (Strakowski, 2011). Even when bipolar subjects were asymptomatic and working on a cognitive task, activity increased in limbic and associated areas (Strakowski, Adler, Holland, Mills, & DelBello, 2004). The researchers suggested that individuals with bipolar I disorder are unable to suppress emotion networks during emotionally neutral activities.

Both depressed and bipolar patients have anomalies in functional brain connectivity. Connectivity is reduced in the cortex, corpus callosum, and thalamus in individuals with bipolar disorder (Barysheva, Jahanshad, Foland-Ross, Altshuler, & Thompson, 2013). In depression, increased as well as decreased connectivity has been reported. For example, one study reported decreased connectivity between frontal areas and the ventral striatum, but increased connectivity between frontal areas and the dorsal striatum (Furman, Hamilton, & Gotlib, 2011). Treatment has been shown to increase deficient connectivity between some areas (Heller et al., 2013) and to decrease excess connectivity in others (Perrin et al., 2012). In both cases, the changes in connectivity were accompanied by symptom improvement.

Suicide

Suicide accounts for more deaths than homicide or war; it is the 13th leading cause of death worldwide and the 4th among those aged 15–44 years (World Health Organization, 2002). Ninety percent of people who attempt suicide have a diagnosable psychiatric illness; mood disorder alone accounts for 60% of all completed suicides (Figure 14.26; Mann, 2003). Bipolar patients are most at risk; about
20% of people who have been hospitalized for bipolar disorder commit suicide. According to the *stress-diathesis model*, the suicidal individual has a predisposition, known as a diathesis, and then stress such as a worsening psychiatric condition acts as an environmental “straw that breaks the camel’s back” (Mann, 2003). The stresses can be physical, as well as psychological, as the accompanying In the News feature illustrates.

The predisposition is at least partly genetic; a study of depressed patients located six chromosome sites that were associated with suicidal risk but independent of susceptibility for mood disorders (Zubenko et al., 2004). Psychiatric patients who attempt suicide also are more likely to have low levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) than non-attempters, which means that their serotonin activity is particularly decreased. When a group of patients at risk for suicide was followed for one year, 20% of those who were below the group median in 5-HIAA level had committed suicide; none of the patients above the median had (Träskman, Åsberg, Bertilsson, & Sjöstrand, 1981). Other studies have confirmed the association between lowered serotonin and suicidality (see Figure 14.27; Mann, 2003; Roy, Delong, & Linnoila, 1989; M. Stanley, Stanley, Traskman-Bendz, Mann, & Meyendorff, 1986). Lowered 5-HIAA is found in suicide attempters with a variety of disorders and probably reflects impulsiveness rather than the patient’s specific psychiatric diagnosis (Mann et al., 1990; M. Stanley et al., 1986; Träskman et al., 1981); this view was supported by a later study in which impulsive suicide attempters were found to have
lower 5-HIAA than either nonimpulsive attempters or controls (Spreux-Varoquaux et al., 2001).

However, antidepressants can increase the risk of suicide. A variety of explanations have been offered, including the agitation that often accompanies SSRI use (Fergusson et al., 2005) and disappointment over slow improvement and side effects (Mann, 2003). Concern about the vulnerability of children and adolescents resulted in a 22% decrease in SSRI prescriptions for youths in the United States and the Netherlands; unfortunately, this turned out to be a case of throwing out the baby with the bathwater, since youthful suicides increased 14% in the United States in one year and 49% in the Netherlands over two years (Gibbons et al., 2007). Some observers believe that the suicidal acts of individuals on antidepressants is the result of rebounding energy levels, which allow those with suicidal ideation the ability to carry out suicidal thoughts. Rather than reducing prescriptions wholesale, therapists need to be selective and to monitor their patients for suicidal tendencies.

Research has identified heritable characteristics that distinguish people at risk for suicide from others, referred to as endophenotypes. The most reproduced personality indicators have been impulsivity and aggression (Courtet, Gottesman, Jollant, & Gould, 2011). Disadvantageous decision making, indicated by measures such as the Iowa Gambling Task, suggest a prefrontal deficiency, and this has been verified in terms of reduced neural activity and altered prefrontal serotonergic functioning. The heritability of suicidal behavior (ideation as well as attempts) has been estimated in various studies at 38%–55% (Brent & Melhem, 2008). Locating genes that predispose a person to suicide has been difficult, in part because of confounding with so many instigators to suicide; these include mental illness, physical illness, and life disappointments. Most studies have pointed to serotonin-related genes and genes involved with brain-derived neurotrophic factors, and a few other genes have been implicated, but there has been little confirmation (S.-J. Tsai, Hong, & Liou, 2011).

CONCEPT CHECK
Take a Minute to Check Your Knowledge and Understanding
• State the monoamine hypothesis; what is the evidence for it?
• How is affective disorder related to circadian rhythms?
• What brain differences are involved in the affective disorders?
• What are some of the factors in suicide?

Anxiety, Trauma, and Stress-Related Disorders

As discussed in Chapter 8, anxiety is the anticipation of some future threat. Anxiety disorders include several illnesses. The major ones—phobia, generalized anxiety, and panic disorder—have lifetime risks of about 13%, 9%, and 6.8%, respectively (Kessler et al., 2012). But their significance lies less in their prevalence than in the disruptiveness of their symptoms. The panic disorder patient or the phobic patient may be unable to venture out of the house, much less hold down a job.

Heredity

Family and twin studies indicate that the anxiety disorders are genetically influenced, with heritability ranging between 20% and 47%, depending on the disorder (Abramowitz, Taylor, & McKay, 2009; P. E. Arnold,
Chapter 14: Psychological Disorders

Understanding the hereditary underpinnings of anxiety is difficult because of significant genetic overlap with other disorders. More than 90% of individuals with anxiety disorders have a history of other psychiatric problems (Kaufman & Charney, 2000). The overlap with mood disorders is particularly strong; 50%–60% of patients with major depression also have a history of one or more anxiety disorders (Kaufman & Charney), and panic disorder is found in 16% of bipolar patients (Doughty, Wells, Joyce, Olds, & Walsh, 2004). Some neural commonality between these two groups is suggested by the effectiveness of antidepressants in treating both mood disorders and anxiety disorders.

The anxieties themselves appear to fall into three genetically related clusters, with generalized anxiety, panic, and agoraphobia (fear of crowds and open places) in one group; animal phobias and situational phobias in the second; and social phobia overlapping genetically with both groups (Hettema, Prescott, Myers, Neale, & Kendler, 2005).

Genetic research has most often implicated genes responsible for serotonin production, serotonin reuptake, and various subtypes of serotonin receptors (reviewed in P. E. Arnold et al., 2004; Rothe et al., 2004; You, Hu, Chen, & Zhang, 2005). Other leads include genes for monoamine oxidase (Tadic et al., 2003), for the adenosine receptor (P. E. Arnold et al.; Lam, Hong, & Tsai, 2005), and for cholecystokinin and its receptor (P. E. Arnold et al.).

Generalized Anxiety, Panic Disorder, and Phobia

Anxiety is often confused with fear; however, as we saw in Chapter 8, fear is a reaction to real objects or events present in the environment, whereas anxiety involves anticipation of events or an inappropriate reaction to the environment. A person with generalized anxiety has a feeling of stress and unease most of the time and

IN THE NEWS
HEIGHTENED SUICIDE RISK AFTER CONCUSSION

Concerns about the cognitive and emotional impacts of brain injury have received a lot of public attention due to well-publicized studies of retired National Football League (NFL) players and military veterans who had been injured due to improvised explosive devices. It now seems clear that the type of repeated injuries that occur in contact sports such as football can result in chronic traumatic encephalopathy (CTE), a progressive degenerative disease of the brain resulting from trauma (Kutner, 2017). One possible effect researchers are investigating is whether head injury increases a person’s risk for suicide. Most media attention has focused on the suicides of retired NFL players such as Junior Seau and Dave Duerson, whose brains showed signs of CTE, but evidence is accumulating from other populations to support a suicide–brain injury link. A study of veterans who had experienced a concussion or cranial fracture found that they were twice as likely to commit suicide as other veterans (Brenner, Ignacio, & Blow, 2011), and a 20-year study reported a tripling of the suicide rate in civilians who had a concussion (Fralick, Thiruchelvam, Tien, & Redelmeier, 2016). Although more investigations are needed, the current data suggest that people who have experienced even one brain injury need to be monitored for long-term affective changes to prevent suicide.

Thought Questions
1. What evidence has shown a link between head injury and suicide risk?
2. How do the types of head injuries experienced by football players differ from those experienced by military veterans and civilians who did not play a contact sport?
3. Which information presented here do you find most convincing of a connection between head injuries and suicides?

For the news story, visit edge.sagepub.com/garrett5e and select the Chapter 14 study resources.
overreacts to stressful conditions. In panic disorder, the person has a sudden and intense attack of anxiety, with symptoms such as rapid breathing, high heart rate, and feelings of impending disaster. A person with a phobia experiences fear or stress when confronted with a situation—for instance, crowds, heights, enclosed spaces, open spaces, or specific objects such as dogs or snakes.

**Neurotransmitters**

Benzodiazepines were the most frequently used anxiolytic (antianxiety) drugs in the past (Costall & Naylor, 1992) but now are considered a second line of defense because of their addiction potential. You may remember from our earlier discussion of drugs in Chapter 5 that benzodiazepines increase receptor sensitivity to the inhibitory transmitter gamma-aminobutyric acid (GABA), which is a major neurotransmitter in anxiety. A deficit in benzodiazepine receptors may be one cause of anxiety disorder. Marczynski and Urbanic (1988) injected pregnant cats with a benzodiazepine tranquilizer. When the offspring were one year old, they were restless and appeared anxious in novel situations. When their brains were studied later, several areas of the brain had compensated for the tranquilizer by reducing the number of benzodiazepine receptors.

Anxiety also appears to involve lower activity at serotonin synapses. Antianxiety drugs initially suppress serotonin activity, but then they apparently produce a compensatory increase. The idea that a serotonergic increase is involved in anxiety reduction is supported by the fact that antidepressants are now the drug of choice for treating anxiety and related disorders.

**Posttraumatic Stress Disorder**

*Posttraumatic stress disorder (PTSD)* is a prolonged stress reaction to a traumatic event; it is typically characterized by recurrent thoughts and images (flashbacks), nightmares, lack of concentration, and overreactivity to environmental stimuli, such as loud noises. Because of recent news coverage, we usually associate PTSD with combat experiences, but it can be triggered by all kinds of trauma, including robbery, sexual assault, hostage situations, and automobile accidents. Men are more often exposed to such traumas, but women are almost four times as likely to develop PTSD when they do experience trauma (Fullerton et al., 2001). PTSD symptoms are resistant to traditional drug and psychotherapy treatments; an alternative approach is exposure therapy, which allows the individual to confront anxiety-provoking stimuli in the safety of the therapist’s office. Exposure therapy is essentially an extinction process, and fear memories are notoriously resistant to extinction, especially in the 30% of people who have the **VAL66MET** allele (which we saw is also involved in depression). We know this gene plays a causal role in fear extinction, because when it was inserted into mice they showed the same increased resistance (Soliman et al., 2010). Brain imaging of human subjects during extinction trials showed why; connections between the prefrontal cortex and the amygdala that are important in fear conditioning and extinction were hypoactive in carriers of the allele.

In their search for better therapies, researchers are resorting to novel approaches; some, for example, believe that therapists could take a lesson from the phenomenon of reconsolidation that you learned about in Chapter 12. A team led by Daniela Schiller (2010) used a mild electric shock to condition an emotional reaction (measured by skin conductance response) to a blue square. A day later, the response was extinguished by repeatedly presenting the blue square alone. However, two subgroups of subjects received a “reminder” of the fear memory, one 10 minutes before extinction began and the other six hours before; the reminder was intended to start reconsolidation, a window of opportunity that was expected to remain open during extinction for the 10-minute group but to be closed by the time the six-hour group’s extinction trials began. It worked: The skin conductance response was almost entirely absent in the 10-minute group but had recovered to near training levels in the other two groups; the effect persisted for a year. Researchers hope this technique of **fear erasure** can be used to help relieve PTSD sufferers of their lingering fear and anxiety.

**Anomalies in Brain Functioning**

For the most part, the various anxiety disorders share a commonality of functional brain anomalies. Not surprisingly, the amygdala is hyperresponsive; the anterior cingulate cortex is hyperactive in general anxiety, panic disorder, and phobias, and the insular cortex is overly responsive in phobias and PTSD (Etkin & Wager, 2007; Morey et al., 2012; Shin & Liberzon, 2010). PTSD is distinguished by decreased activity in the medial prefrontal cortex and, according to some studies, in the hippocampus. Some structures have been reported to be smaller in people with anxiety disorders, particularly in those with PTSD. Researchers have usually assumed these variations were the result of the anxiety disorders, but we will see that this is not always the case.
Whether trauma is followed by PTSD is unrelated to either the severity of the traumatic event or the individual’s distress at the time (Harvey & Bryant, 2002; Shalev et al., 2000); the key apparently is the person’s vulnerability. Mark Gilbertson and his colleagues (2002) used magnetic resonance imaging to measure hippocampal volumes in Vietnam combat veterans and their noncombat identical twins. Those who suffered from PTSD had smaller hippocampi than did PTSD-free veterans, as expected, but so did the PTSD subjects’ noncombat twins (Figure 14.28). Hippocampal reduction is often associated with childhood abuse, and Elizabeth Binder and her coworkers (2008) found that previously abused individuals were twice as likely to succumb to PTSD following traumatic events. Two mutations of the FKBP5 gene are more common among PTSD patients who were abused and apparently contribute to the vulnerability (Binder et al.). A smaller anterior cingulate cortex (ACC) may also be a vulnerability factor. After the Japanese earthquake and tsunami in 2011, researchers at Tohoku University asked 42 local residents who had previously received MRI scans to return and have their brains imaged again. Though none of the residents had full-blown PTSD, those with the highest scores had lower gray matter volumes in the orbitofrontal cortex and in the ACC, compared with control subjects (Sekiguchi et al., 2013). Reduced volume in the orbitofrontal cortex had occurred since the first scan, but the high-scoring subjects had lower ACC volume at the time of the first scan; this suggests that a smaller ACC is a vulnerability factor for PTSD. This makes sense, because the ACC is involved in the processing of fear and anxiety and in eliminating fear-related memories.

Of course, these structures operate as part of circuits, rather than in isolation from each other or other parts of the brain. Chad Sylvester and his colleagues (2012) have identified four networks whose faulty performance they believe contributes to anxiety (Figure 14.29). The ventral attention network orients to attention-demanding stimuli and in people with anxiety disorders contributes to excessively stimulus-driven attention. Once a response to a situation is formulated, a salience network provides error detection by comparing the intended response with appropriate responses. A mismatch would signal the need for increased executive control, the domain of the frontoparietal network. Finally, the default mode network engages in self-monitoring, future planning, and emotion regulation; underactivity in this network results in poor emotional regulation.

CONCEPT CHECK

**Take a Minute to Check Your Knowledge and Understanding**

- What neurotransmitter deviations are involved in anxiety disorders?
- What brain anomalies are associated with anxiety disorders?
- What are the environmental, physiological, and genetic contributors to PTSD?

**Personality Disorders**

The personality disorders are a group of 10 related disorders characterized by a relatively inflexible pattern of behavior that is different from one’s peers, has an onset around puberty to young adulthood, and causes distress or inability to function in society. Typical behavior patterns include distrust and suspicion (paranoid), unstable social and interpersonal relationships (asocial, avoidant, dependent, borderline), problems with control and attention (obsessive-compulsive), and emotional dysfunctions (histrionic, narcissistic). An abnormal psychology course will likely cover most of these personality disorders, but in this text we
will concentrate on two types: obsessive-compulsive disorder and related disorders, and borderline personality disorder.

**Obsessive-Compulsive Disorder**

**Obsessive-compulsive disorder (OCD)** consists of two behaviors, obsessions and compulsions, which occur in the **same person**. The disorder affects about 2.6% of the population over their lifetimes (Kessler et al., 2012). An **obsession** is a recurring, uncontrollable thought; a person may be annoyed by a tune that mentally replays over and over or by troubling thoughts such as wishing harm to another person. Normal people have similar thoughts, but for the obsessive individual, the experience is extreme and feels completely out of control. Just as the obsessive individual is a slave to thoughts, the compulsive individual is a slave to actions. **Compulsions** are ritualistic behaviors that must be done to remove the anxiety of the obsession, such as touching a door frame three times before passing through the door, endless bathing and hand washing, or checking to see if appliances are turned off and the door is locked (Rapoport, 1991). Prominent examples of this disorder are depicted in the films *As Good as It Gets* and *The Aviator* and in the television show *Monk*.

One psychiatrist described a patient who tired of returning home to check whether she had turned her appliances off and solved the problem by taking her coffeemaker and iron to work with her (Begley & Biddle, 1996). The playwright and humorist David Sedaris (1998) wrote that his short walk home from school during childhood took a full hour because of his compulsion to stop every few feet and press his nose to the hood of a particular car, lick a certain mailbox, or touch a specific leaf that demanded his attention. Once home, he had to make the rounds of several rooms, kissing, touching, and rearranging various objects before he could enter his own room. About a fourth of OCD patients have a family member with OCD, suggesting a genetic involvement; boys are afflicted more often than girls, but the ratio levels off in adulthood (Swedo, Rapoport, Leonard, Lenane, & Cheslow, 1989).

What about individuals who are obsessed with neatness, organization, and generally making sure that their world is “where it should be?” This is not OCD, but a related disorder called obsessive-compulsive personality disorder (OCPD), in which the person does not experience the distress and anxiety over obsessively cleaning and
organizing that someone with OCD would experience. Instead, those feelings of perfection are perceived to be rational and reasonable. OCPD is much harder to treat, compared to OCD.

Imaging studies of OCD patients reveal increased activity in the orbitofrontal cortex, especially the left orbital gyrus, and in the caudate nuclei (Whiteside, Port, & Abramowitz, 2004). It is unclear whether these increases cause OCD or are merely activation increases associated with symptoms of OCD, such as worry. However, both drug treatment and behavior therapy reduce activation of the caudate nucleus and, in at least one study, the orbital gyrus (Figure 14.30; Porto et al., 2009; J. M. Schwartz et al., 1996; Swedo, Schapiro, et al., 1989). White matter reductions indicate that there are deficient connections between the cingulate gyrus and a circuit involving the basal ganglia, thalamus, and cortex, which apparently result in a loss of impulse control (Insel, 1992; Szaszko et al., 2005). An indication of dysfunction in this network is that orbitofrontal activity does not increase when OCD patients are required to reverse a previously correct choice; their unaffected relatives show the same deficit, suggesting that it is genetic (Chamberlain et al., 2008).

OCD occurs with several diseases that damage the basal ganglia (H. L. Leonard et al., 1992), which you will remember, are involved in motor activity. There is growing evidence that the disorder can be triggered in children by a bacterial infection that results in an autoimmune attack on the basal ganglia; vulnerability to the immune malfunction apparently is hereditary (P. D. Arnold & Richter, 2001; P. E. Arnold et al., 2004). OCD has also been reported in cases of head injury (McKeon, McGuffin, & Robinson, 1984). Two of the most famous obsessive-compulsive individuals had a strong germ phobia (called mysophobia); the multimillionaire Howard Hughes (R. Fowler, 1986) and the star of the television show Deal or No Deal, comedian Howie Mandel (Mandel, 2010). In Hughes’s case, some signs of disorder during childhood and his mother’s obsessive concern with germs suggest either genetic vulnerability or environmental influence. However, symptoms of OCD did not begin until after a series of airplane crashes and automobile accidents that left him almost unrecognizable (Figure 14.31). When a business associate died, Hughes gave explicit instructions that flowers for the funeral were to be delivered by an independent messenger who would not have any contact with the florist or with Hughes’s office—even to the point of sending a bill—to prevent “backflow” of germs (Bartlett & Steele, 1979). Assistants were required to handle his papers with gloves, sometimes several pairs, and he in turn grasped them with a tissue. He instructed his assistants not to touch him, talk directly to him, or even look at him; his defense for this behavior was that everybody carries germs and he wanted to avoid germs (R. Fowler).

![FIGURE 14.30 Brain Structures Involved in Obsessive-Compulsive Disorder.](attachment:brain_structures.png)

Scans of OCD patients show that (a) activity is elevated in the caudate nucleus (a part of the basal ganglia) and in the orbital gyrus, and that (b) behavior therapy reduces this activity in the caudate nucleus.

Researchers believe that OCD patients are high in serotonergic activity. This was suggested by the fact that people with OCD are inhibited in action and feel guilty about aggressive impulses; sociopaths, by contrast, feel no guilt after committing impulsive crimes, and they have lowered serotonin activity. But the only drugs that consistently improve OCD symptoms are antidepressants that inhibit serotonin reuptake (Insel, Zohar, Benkelfat, & Murphy, 1990). So, if OCD patients do have high serotonergic activity, then reuptake inhibitors must work by causing a compensatory reduction in activity; there is some evidence that treatment does decrease the sensitivity of serotonin receptors (Insel et al., 1990), but the nature of serotonin involvement remains uncertain (Graybiel & Rauch, 2000).

Patient response to serotonin reuptake inhibitors is usually only partial, and some patients do not respond at all; a third of these patients benefit from antipsychotics, and an antiglutamate drug produces modest relief (Abramowitz et al., 2009), suggesting the involvement of these transmitters. For treatment-resistant patients, psychosurgery is an option. Forty-seven percent of patients went into remission following cingulotomy, which involves lesioning the ACC, and another 22% improved (Sheth et al., 2013). A less drastic procedure is deep brain stimulation (DBS), targeting the internal capsule, a bundle of fibers that connect the frontal lobe with the thalamus and other areas. A DBS device was approved by the U.S. Food and Drug Administration (2009) after it produced a 40% reduction in symptoms in OCD patients.

A meta-analysis of 113 studies found associations with two serotonin genes and, in males only, two genes involved in degradation of dopamine and serotonin (S. Taylor, 2013). There were trends for two dopamine-related genes and a glutamate-related gene, but these were not statistically significant. The rate of disorders in relatives of people with OCD suggests a genetic association with anxiety disorders, depression, tic disorders such as Tourette syndrome (discussed later), and grooming disorders such as hair pulling and skin picking (Bienvenu et al., 2012).

OCD-Related Disorders

The symptoms of OCD, particularly washing and “grooming” rituals and preoccupation with cleanliness, suggest to some researchers that it is a disorder of “excessive grooming” (H. L. Leonard, Lenane, Swedo, Rettew, & Rapoport, 1991; Rapoport, 1991). Dogs and cats sometimes groom their fur to the point of producing bald spots and ulcers in a disorder known as acral lick syndrome. Some chimpanzees and monkeys engage in excessive self-grooming and hair pulling, and 10% of birds in captivity compulsively pull out their feathers, occasionally to the point that the bird is denuded and at risk for infection and hypothermia. Clomipramine, an antidepressant that inhibits serotonin reuptake, is effective in reducing all these behaviors (Grindlinger & Ramsay, 1991; Hartman, 1995; Rapoport, 1991). If you think that the excessive grooming idea sounds far-fetched, consider the human behaviors of nail biting and obsessive hair pulling (trichotillomania), in which the person pulls hairs out one by one until there are...
visible bald spots or even complete baldness of the head, eyebrows, and eyelashes. There are several similarities between hair pulling and OCD: Both behaviors appear to be hereditary, and hair pullers have a high frequency of relatives with OCD; both symptoms also respond to serotonin reuptake inhibitors (Leonard et al., 1991; Swedo et al., 1991). However, trichotillomania and OCD sufferers appear to differ from each other in their versions of the Sapap3 gene (Bienvenu et al., 2008). The gene's normal role is most likely a protective one, since mice that lack the gene groom to the point of self-injury; their behavior is relieved by a serotonin reuptake inhibitor (Figure 14.32; J. M. Welch et al., 2007).

Hoarders are dedicated collectors, stashing away just about anything from string to old newspapers. People with OCD are often hoarders as well, but hoarding disorder is considered distinct from OCD. David Tolin and his colleagues (2012) placed people with hoarding disorder in an fMRI scanner and had them look at pictures of junk mail and newspapers and decide whether to keep or discard them. The subjects had brought 50 of the items from home, and another 50 were provided by the experimenters. Hoarders, people with OCD, and healthy controls all were willing to discard more than 40 of the 50 items that were not theirs.

**APPLICATION**

Of Hermits and Hoarders

There is greater awareness about hoarding disorder because of documentary TV series such as Hoarders, which profiles extreme hoarders; in one segment, the home is so cluttered that people take meals in bed (Weiss, 2010). In each episode, clinicians and professional organizers, with the aid of friends and family, assist the hoarder in the cleanup of his or her home. The intervention is usually precipitated by a crisis, such as a threat to remove the children for health and safety reasons. Hoarding can be so extreme that it poses broader dangers as well; for example, 14 firefighters were injured when 150 of them were called to put out a fire in a New York City apartment filled with floor-to-ceiling junk (Newman, 2006).

But the most severe hoarders that we know about may be the Collyer brothers, Homer and Langley. They grew up in a Fifth Avenue New York City mansion with their eccentric first-cousin parents; their father, a gynecologist, canoed to work at Bellevue Hospital and the family gave up their telephone, electricity, and gas to “simplify” their lives (Weiss, 2010). Homer became an attorney, and Langley graduated from Columbia University in mechanical engineering and chemistry and then tried a career as a concert pianist. After their parents died, the two brothers became reclusive hermits. Homer was confined to the home by blindness and arthritis, but Langley busied himself with nighttime treks through the neighborhood collecting odds and ends off the streets. On March 21, 1947, responding to a tip about an odor, police broke into the mansion through a second-story window after finding the foyer blocked by a solid wall of junk (“Collyer Brothers,” n.d.). They found Homer dead of starvation and no sign of Langley. The home was so cluttered that Langley had made tunnels through the debris in order to move from room to room; some of those tunnels were rigged with booby traps as a defense against intruders. Authorities removed the contents from the home; 18 days after Homer’s body was discovered, Langley was found just 10 feet away, crushed under one of his own traps. There was so little of value in the 130 tons of material that was removed from the home that an auction brought little money. For the next decade, children grew up with their mothers’ admonition, “Clean up your room or you’ll end up like the Collyer brothers!” (Weiss, p. 251).
When it came to their own items, the healthy controls discarded 40 and those with OCD discarded 37, but the hoarders gave up only 29. More telling, during this part of the study the hoarders reported “not feeling right” and showed more activity than the others in the ACC, which evaluates behavior and detects errors, and in the insula, which is important to a sense of self. Apparently, giving up these possessions was threatening; this can lead to really bizarre behavior, as the accompanying Application reveals.

Another disorder associated with OCD is Tourette syndrome, whose victims suffer from a variety of motor and phonic (sound) tics. They twitch and grimace, blink their eyes rapidly, throw punches at the air, cough, grunt, bark, echo what others say, mimic peoples’ facial expressions and gestures, and (rarely) blurt out derogatory remarks and profanity. Both OCD and Tourette sufferers can manage their symptoms for short periods; for instance, Tourette patients are usually symptom free while driving a car, having sex, or performing surgery (yes, some of them are surgeons!). But neither OCD nor Tourette is a simple matter of will: Children often suppress compulsive rituals at school and “let go” at home, or they suppress tics during the day and then tic during their sleep. Neurologist Oliver Sacks (1990) graphically describes a woman on the streets of New York who was imitating other people’s expressions and gestures as she passed them on the sidewalk:

Suddenly, desperately, the old woman turned aside, into an alleyway which led off the main street. And there, with all the appearances of a woman violently sick, she expelled . . . all the gestures, the postures, the expressions, the demeanours, the entire behavioural repertoires, of the past forty or fifty people she had passed. (p. 123)

Symptoms begin between the ages of 2 and 15 years and usually progress from simple to more complex tics, with increasing compulsive or ritualistic qualities. The incidence of Tourette is difficult to determine; in recent studies the numbers have varied from 3 to 8 per 1,000 persons. In a survey of 64,000 children in the United States, the rate was 3 out of every 1,000, with three times as many males as females (Scahill, Bitsko, Visser, & Blumberg, 2009). Tourette syndrome is genetically influenced, with a concordance rate of 53% for identical twins and 8% for fraternal twins (R. A. Price, Kidd, Cohen, Pauls, & Leckman, 1985). Tourette shares some genetic roots with OCD; a third of patients with early-onset OCD also have Tourette syndrome (do Rosario-Campos et al., 2005), and 30% of adults with Tourette are also diagnosed with OCD (R. A. King, Leckman, Scahill, & Cohen, 1998). Recent studies have identified a mutation of the SLITRK1 gene in Tourette and found a mutation of the Hdc gene in a man and his eight offspring, all of whom have the disorder (Abelson et al., 2005; Ercan-Sencicek et al., 2010). The genes function in neural development and transmission, and both are highly active in brain areas involved in Tourette.

Tourette syndrome, like OCD, involves increased activity in the basal ganglia. But unlike OCD, the most frequently prescribed drug for Tourette is an antidopaminergic drug, haloperidol, though newer antidopaminergic drugs are also being used. One effect dopamine has is motor activation, and Malison and his colleagues (1995) found that dopamine activity is elevated in Tourette sufferers in the caudate nuclei of the basal ganglia (Figure 14.33). There has been some success treating Tourette with deep brain stimulation to the thalamus, which suppressed tics and produced feelings of calmness (Okun et al., 2013).

### Borderline Personality Disorder

To finish up our tour of the psychological disorders, we end with one of the most intriguing personality disorders: borderline personality disorder (BPD). This condition, which affects 0.5–5.9% of the population (Grant et al., 2008), is characterized by unstable interpersonal relationships, poor self-image, and impulsivity. Individuals with this condition have an intense fear of abandonment and rejection and an equally strong desire to be loved. They often switch between intense feelings of “love” and “hate,” they engage in risky behaviors such as gambling and speeding, and they are at a very high risk for suicide and suicidal thoughts. In fact, 8%–10% of individuals with BPD kill themselves, and they are prone to taking medication far beyond the recommended dose in committing suicide.
BPD has a strong genetic basis, with a heritability about 40% (Amad, Ramoz, Thomas, Jardri, & Gorwood, 2014). Genes linked to BPD include ones responsible for serotonin receptors, serotonin transporters such as SHTTLPR, dopamine transporters such as DAT1, and enzymes that make neurotransmitters (such as tyrosine hydroxylase), as well as genes that influence neuronal survival (brain-derived neurotrophic factor) and neuronal death (see Amad et al., 2014, for a review of the research that led to these conclusions). Therefore, BPD appears to be caused by dysfunction of both serotonin and dopamine neurotransmitter systems, as well as by decreases in neuronal number. Of interest was a finding that the MAOA gene (discussed in Chapter 8) is linked to both aggressive behaviors and borderline personality disorder (Craig & Halton, 2009). Even with these genetic correlates, the remaining 60% of the disorder likelihood is environmental; indeed, psychiatrists believe the genes predispose an individual toward the imbalance of BPD but that a set of environmental events must happen to activate the epigenetic changes that result in the disorder (Figure 14.34).

**CONCEPT CHECK**

Take a Minute to Check Your Knowledge and Understanding

- Describe the symptoms of OCD and the related disorders.
- What are the distinguishing characteristics of borderline personality disorder?
- What treatments are used with these disorders?

**In Perspective**

The past several decades have seen enormous progress in research, and we now know a great deal about the physiological causes of disorders. We owe these breakthroughs to advances in imaging techniques and genetics research technology and to our greatly improved understanding of the physiology of synapses, not to mention the persistence of dedicated researchers. The result is that we can now describe at the biological level...
many disorders that previously were believed to be "psychological" in origin or that were only suspected of having an organic basis.

Despite these great research advances, we cannot reliably distinguish the schizophrenic brain from a normal one, or diagnose psychological disorders from a blood test. We may be able to someday, but in the meantime, we rely on changes in behavior of the individuals for a disorder diagnosis. This can be difficult, because these disorders frequently share common features (for example, schizophrenia, mood disorders with psychotic features, and bipolar I disorder). We know, at least to some extent, the physiological components of mental illness, but we do not understand the unique combination of physiological and environmental factors that determines who will suffer from a disorder and who will not. If that is true, our treatments will remain a pale hope rather than a bright promise.

We have been reminded repeatedly that genetic vulnerability is not the same thing as fate. In most cases, the genes produce an illness only with the cooperation of the environment. This point is emphasized by the fact that psychotherapy and cognitive-behavioral therapy play an important role in treatment, enhancing and frequently exceeding the benefit that drugs can provide (see Durand & Barlow, 2006). While we search for genetic treatments of the disorders, we must remind ourselves once again that heredity is not destiny; improving the physical and psychological welfare of the population would go a long way toward preventing mental illness or reducing its severity.

Just before the dawning of this new age of research, one frustrated schizophrenia researcher concluded, "Almost everything remains to be done" (Heston, 1970, p. 234). Since then our knowledge of both the brain and its participation in the symptoms of mental illness has increased dramatically, but as you can see, much of our understanding remains tentative. The pace is quickening, and we are confident that in this second decade of the new millennium, we will be celebrating even more impressive advances than in the past.

CHAPTER SUMMARY

Schizophrenia

- Schizophrenia is characterized by a mix of positive and negative symptoms such as hallucinations, delusions, thought disorder, and social and emotional withdrawal.
- Twin and adoption studies indicate that heritability is .60 to .90. Genetic influences involve many small-effect genes and rarer copy number variations with stronger effects. Genes apparently determine the level of vulnerability.
- Positive and negative symptoms may be distinguished by excess dopamine activity versus brain deficits.
- Although there is evidence for the dopamine hypothesis, it is an incomplete explanation. The glutamate hypothesis is getting more attention because NMDA receptor antagonists produce symptoms of schizophrenia and drugs that activate NMDA receptors relieve them.
- The brain irregularities include ventricular enlargement (due to tissue deficits), hypofrontality, and impaired connections; these apparently arise from prenatal insults and impaired postnatal development, in interaction with genetic vulnerability. Reduced connectivity and impaired synchrony between areas are also involved.
- Maternal effect from illnesses such as influenza and prenatal starvation are examples of environmental influences.

Affective Disorders

- The affective disorders include depression, mania, and bipolar disorder, an alternation between mania and depression.
- The affective disorders are also highly heritable, especially for women. Some genes are shared with schizophrenia, ASD, and ADHD.
- The most prominent explanation of affective disorders is the monoamine hypothesis—an imbalance in serotonin and epinephrine.
- Electroconvulsive therapy is a controversial but very effective last-resort therapy that has value when medications fail and as a temporary suicide preventative; both drugs and ECT increase neurogenesis and neural plasticity.
- People with affective disorders often have circadian rhythm disruptions. Others respond to circannual changes with winter depression or summer depression.
- Bipolar disorder is now considered to be a separate group of disorders, and is the bridge disorder between schizophrenia and depression.
- Bipolar disorder is less understood than unipolar depression. Response to atypical antipsychotics suggests involvement of dopamine and, possibly, serotonin.
- A number of brain anomalies distinguish depressed people from bipolar patients and both from normal people.
- Depression, low serotonin activity, and several genes are associated with suicide risk.

Anxiety, Trauma, and Stress-Related Disorders

- The anxiety disorders are characterized mostly by brain hyperresponsiveness, but activity is decreased in some areas in posttraumatic stress disorder.
- Anxiety involves low serotonin activity; GABA transmission and benzodiazepine receptor deficiency may also be involved.
- The anxiety disorders are partially hereditary, and the serotonin system is most often implicated. There is considerable overlap with mood disorders.
Personality Disorders

- In obsessive-compulsive disorder, activity is increased in the orbitofrontal cortex; deficient connections with the cingulate gyrus apparently reduce impulse control.
- OCD is associated with grooming disorders.
- Tourette syndrome shares some genetic roots with OCD, but OCD appears to involve high serotonin activity, whereas Tourette is treated with dopamine antagonists.
- In borderline personality disorder, there is a strong tendency for impulsivity, rapid emotional swings, and a series of damaging and maladaptive behaviors like cutting, suicide, and risky behaviors.
- BPD is thought to occur through the epigenetic activation of genes related to serotonin, dopamine, and aggression systems.

Studying Resources

For Further Thought

- Now that we are nearing the end of the text, summarize what you know about the interaction of heredity and environment. Give examples from different chapters and include the concept of vulnerability.
- Give an overall view of what produces deviant behavior (going back to earlier chapters as well as this one). What effect does this have on your ideas about responsibility for one's behavior?
- Behavior is vulnerable to a number of disturbances, involving both genetic and environmental influences. Consider the different ways complexity of the brain contributes to this vulnerability.

Test Your Understanding

1. Explain the dopamine theory of schizophrenia. What are its deficiencies? What alternative or complementary explanations are available?
2. Describe the monoamine hypothesis of depression; include the evidence for it and a description of the effects of the drugs and ECT used to treat depression.
3. Describe the similarities and associations among OCD, Tourette, and “grooming” behaviors.

Select the best answer:

1. If you were diagnosed with schizophrenia, you should prefer _____ symptoms.
   a. positive  
   b. negative  
   c. chronic  
   d. bipolar

2. The fact that schizophrenia involves multiple genes helps explain
   a. vulnerability to winter viruses.  
   b. the onset late in life.  
   c. positive symptoms.  
   d. different degrees of vulnerability.

3. All drugs that are effective in treating schizophrenia
   a. interfere with reuptake of dopamine.  
   b. have some effect at D2 receptors.  
   c. stimulate glutamate receptors.  
   d. inhibit serotonin receptors.

4. Schizophrenia apparently involves
   a. tissue deficits.  
   b. frontal dysfunction.  
   c. disrupted connections.  
   d. a and b  
   e. a, b, and c

5. Which disorder is the bridge between schizophrenia and depressive disorders?
   a. Borderline personality disorder  
   b. Obsessive-compulsive disorder  
   c. Bipolar disorder  
   d. Posttraumatic stress disorder

6. The monoamine hypothesis states that depression results from
   a. reduced activity in norepinephrine and serotonin synapses.  
   b. increased activity in norepinephrine and serotonin synapses.  
   c. reduced activity in norepinephrine, serotonin, and dopamine synapses.  
   d. increased activity in norepinephrine, serotonin, and dopamine synapses.

7. ECT appears to relieve depression by
   a. producing amnesia for depressing memories.  
   b. the same mechanisms as antidepressant drugs.  
   c. punishing depressive behavior.  
   d. increasing EEG frequency.

8. A frontal area hypothesized to switch between depression and mania is the
   a. dorsolateral prefrontal cortex.  
   b. caudate nucleus.  
   c. ventral prefrontal cortex.  
   d. subgenual prefrontal cortex.
9. Studies indicate that risk for suicide is related to
   a. low norepinephrine and serotonin.
   b. high norepinephrine and serotonin.
   c. low serotonin.
   d. low norepinephrine.

10. The anxiety disorders are associated genetically with
    a. schizophrenia and depression.
    b. schizophrenia.
    c. depression.
    d. none of these

11. Of these, the best predictor of PTSD following trauma is
    a. a history of childhood abuse.
    b. being male.
    c. the severity of the trauma.
    d. the intensity of the reaction to the trauma.

12. Both OCD and Tourette syndrome involve compulsive rituals, probably because they involve
    a. increased dopamine.
    b. increased activity in the basal ganglia.
    c. a stressful home life.
    d. all of these

13. Instability of emotion is a hallmark of
    a. bipolar II disorder
    b. PTSD
    c. OCPD
    d. borderline personality disorder

Answers:
1. a, 4, 2, 3, 6, 7, 8, 9, 10, 11, 12, 13

ON THE WEB

The following websites are coordinated with this chapter’s content. You can access these websites from the SAGE edge Student Resources site; select this chapter and then click on Web Resources. (Bold items are links.)

1. I and I, Dancing Fool, Challenge You the World to a Duel is Ian Chovil’s account of his schizophrenia, bizarre delusions, and homelessness. Coping much better on olanzapine, he now works part time educating the public about the illness.
   An online version of the Wisconsin Card Sorting Test is available at PsyToolkit’s website. In addition, that free site has many other psychological experiments you can perform.

2. PsychCentral offers an online Depression Screening Test to help a person assess his or her symptoms.

3. MD Junction and DailyStrength provide discussion groups for people affected by SAD and information about the disorder.

4. The Depression and Bipolar Support Alliance site is a place to learn about mood disorders and ongoing research and to take a mood disorders questionnaire.

5. At Hoarders, you can watch entire episodes of the reality TV series if you don’t have time for that, sample a few and read descriptions of the people for insights into the lives of hoarders and their families.

6. The Tourette Association of America is a good resource for information on this disorder.

7. The Mighty has a great selection of resources on borderline personality disorder, as well as autism, mental illness, and how these affect parents and caregivers.

FOR FURTHER READING

1. When the Music’s Over: My Journey Into Schizophrenia, by Ross Burke (Plume/Penguin, 1995), is the author’s account of his battle with schizophrenia, published by his therapist after Burke ended the battle with suicide.

2. An Unquiet Mind, by Kay Jamison (Knopf, 1995), tells the story of her continuing battle with bipolar disorder, which rendered her “ravishingly psychotic” three months into her first semester as a psychology professor. With the aid of lithium, she has become an authority on mood disorders.

3. Abnormal Psychology, by William Ray (SAGE, 2015), is a text written with a neuroscience perspective.

4. Here’s the Deal: Don’t Touch Me, by Howie Mandel (Bantam, 2010), is a fascinating memoir of the comedian’s lifelong struggle with OCD, and the effect it has had not only on his own life but also on the lives of those around him.

5. “All in the Mind of a Mouse,” by Carina Dennis (Nature, 2005, 438, 151–152), is an intriguing look at the creative ways researchers are using mice to study human psychological disorders.

6. “I Hate You—Don’t Leave Me” by Jerold J. Kreisman (TarcherPerigee, 2010), is an amazing view into what someone with borderline personality disorder goes through, written by
a clinician who founded the world's first care facility specifically for individuals struggling with the disorder.

7. If you are interested in the most up-to-date description of medications currently being prescribed to combat various disorders, the *Handbook of Clinical Psychopharmacology for Therapists* (7th edition), by John Preston and colleagues (New Harbinger Publications, 2012), is a wonderful and inexpensive resource.

**KEY TERMS**

- aberrant salience hypothesis 412
- acute 408
- bipolar disorder 421
- chronic 408
- circadian rhythm 427
- circannual rhythm 428
- depression 428
- dopamine hypothesis 412
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SAGE edge offers a robust online environment featuring an impressive array of free tools and resources for review, study, and further exploration, keeping both instructors and students on the cutting edge of teaching and learning.