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Chapter Summary

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After reading this chapter, you will be able to:

- Name and describe the various categories of psychological disorders.
- Understand the 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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Bob 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.

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

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, Schüttler, & 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 (Nemadé & 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 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

FIGURE 14.1 Psychological Disorders Impair a Person's Ability to Cope.



Source: Cheryl Chan/Moment/Getty.

? What is schizophrenia, and what causes it?

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FIGURE 14.1 Psychological Disorders Impair a Person's Ability to Cope.



Source: Cheryl Chan/Moment/Getty.



What is schizophrenia, and what causes it?

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.

“
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*

Heredity

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.

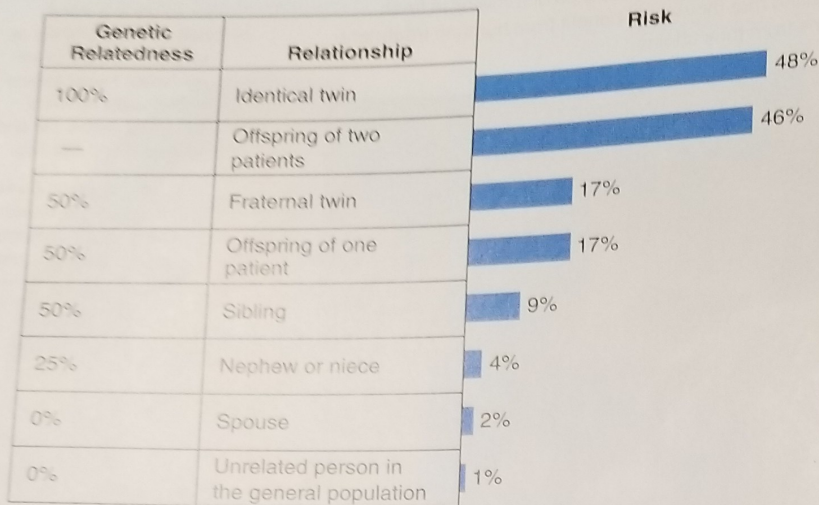
Twin and Adoption Studies

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.



Source: From *Introduction to Psychology, Gateways to Mind and Behavior* (with InfoTrac), 9th edition by Coon, 2001. Reprinted with permission of Wadsworth, a division of Thomson Learning.

of the nonschizophrenic twins have spectrum disorders (Heston; Onstad, Skre, Torgersen, & 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

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%

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).

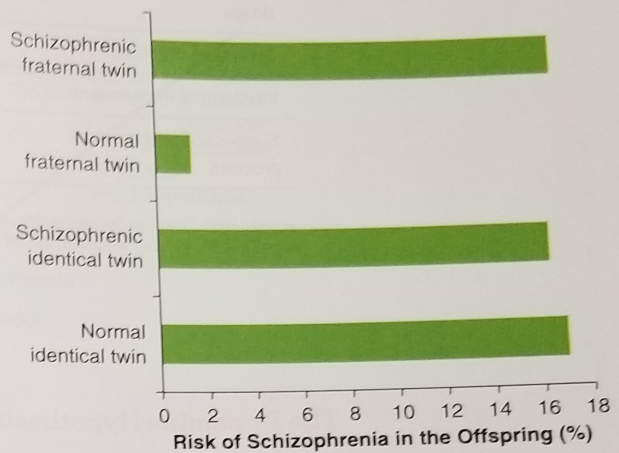
Two Kinds of Schizophrenia

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.

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”

ASPECT		
Characteristic symptoms	Delusions, hallucinations, etc.	Poverty of speech, lack of affect, etc.
Response to antidopaminergic drugs	Good	Poor
Symptom outcome	Potentially reversible	Irreversible?
Intellectual impairment	Absent	Sometimes present
Suggested pathological process	Increased D ₂ dopamine receptors	Cell loss in temporal lobes

Source: From "The Two-Syndrome Concept: Origins and Current Status," T. J. Crow, 1985, *Schizophrenia Bulletin*, 11, pp. 471–486, with permission of Oxford University Press.

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).

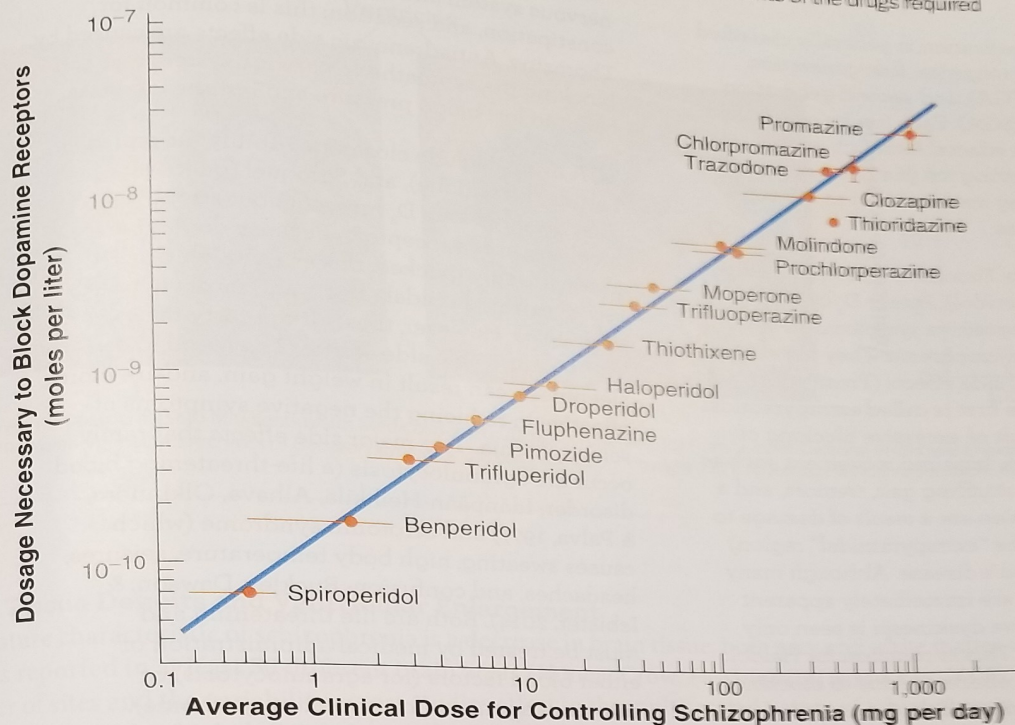
Beyond the Dopamine Hypothesis

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

FIGURE 14.7 Relationship Between Receptor Blocking and Clinical Effectiveness of Schizophrenia Drugs.

The horizontal axis is the average daily doses prescribed by physicians; the horizontal red lines represent typical ranges of doses used. Values on the vertical axis are amounts of the drugs required to block 50% of the dopamine receptors.



Source: Reprinted by permission from "Antipsychotic Drug Doses and Neuroleptic/Dopamine Receptors," by P. Seeman et al., *Nature*, 261, p. 718, fig. 1. Copyright 1976 Macmillan Publishers, Ltd.

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 D_2 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 D_2 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; Leucht et al., 2009; 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 D_2 receptors are therapeutically ineffective (H. M. Jones & Pilowsky, 2002). So, successful therapy apparently requires D_2 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 $5-HT_{2A}$ receptor's involvement in schizophrenic-like responses to hallucinogenic drugs, such as psilocybin and LSD. The number of $5-HT_{2A}$ receptors is upregulated in the brains of deceased schizophrenic subjects (González-Maeso et al., 2008), and atypical antipsychotics block serotonin $5-HT_2$ 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 D_2 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 D_2 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; Idänpään-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).

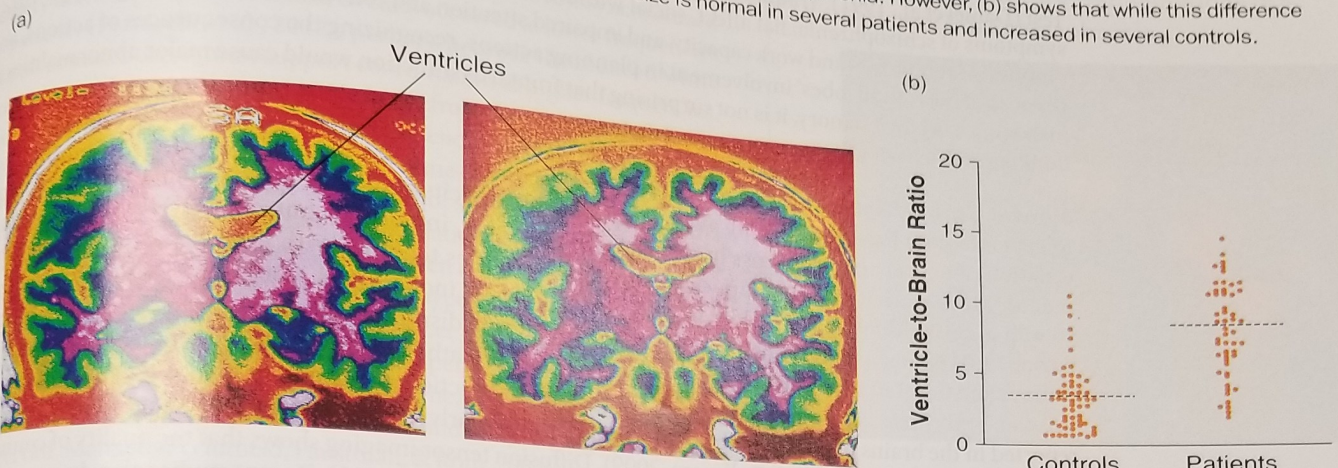
(H. M. Jones & Pilowsky, 2002; Kapur, Zipursky, & Remington, 1999). But serotonin has not received nearly as much attention as glutamate activity, which also is affected by atypical antipsychotics. The drug phencyclidine (PCP), which inhibits the NMDA (*N*-methyl-*D*-aspartic acid) subtype of glutamate 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.

FIGURE 14.8 *Ventricle Size in People With and Without Symptoms of Schizophrenia.*
 In two identical twins (a) the lateral ventricles are larger in the one with schizophrenia. However, (b) shows that while this difference is true on average (indicated by the dotted lines), ventricle size is normal in several patients and increased in several controls.



Sources: (a) Copyright 1990 Massachusetts Medical Society. All rights reserved. (b) From "Lateral Cerebral Ventricular Enlargement in Chronic Schizophrenia," by D. R. Weinberger et al., *Archives of General Psychiatry*, 36, pp. 735–739. Copyright 1979 American Medical Association. Reprinted with permission.

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, the 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 frontal 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 lighting up during the

? What brain defects have been found in schizophrenia?

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 concentration (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.

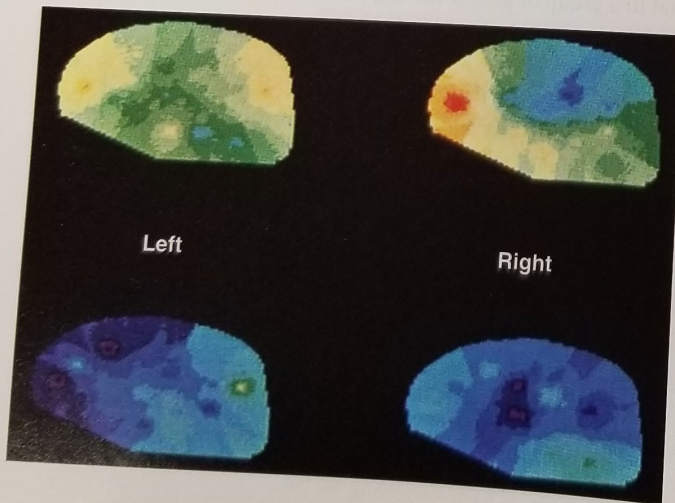
Neural Connections and Synchrony

Recent attention has been shifting away from localized deficits and focusing instead on disrupted coordination 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 hippocampus 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 connections is compromised throughout much of the brain (B. R. Lee et al., 2013). Recent studies also documented 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). 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.

FIGURE 14.9 Blood Flow in Normal and Schizophrenic Brains During Card Sorting Test.

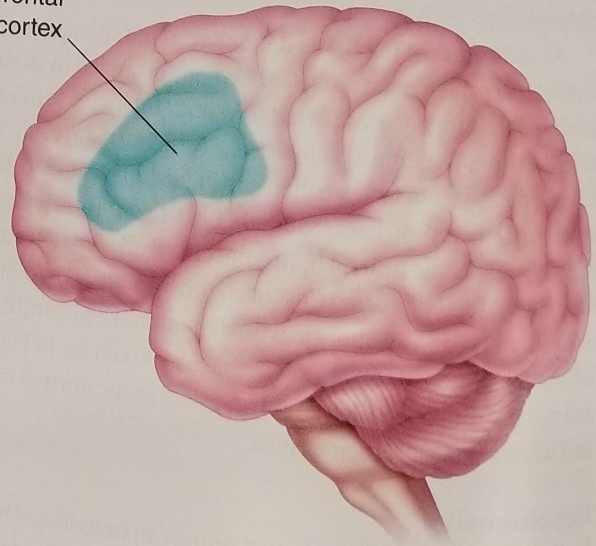
(a) The upper images are of the left and right hemispheres of a normal brain; the schizophrenic brain is below. Red and yellow represent greatest activation. Note especially the activity in the dorsolateral prefrontal cortex, whose location is identified in (b).

(a)



(b)

Dorsolateral
prefrontal
cortex



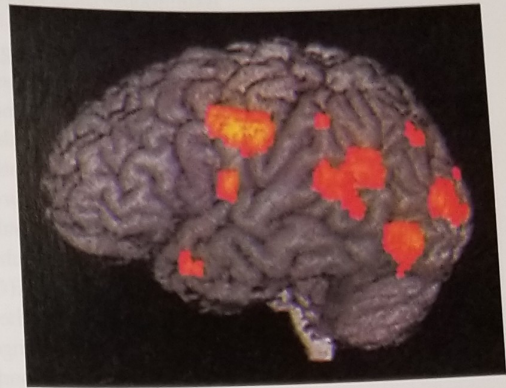
Source: (a) From "Physiologic Dysfunction of Dorsolateral Prefrontal Cortex in Schizophrenia: I. Regional Cerebral Blood Flow Evidence," by D. R. Weinberger, K. F. Berman, and R. R. Zec, 1986, *Archives of General Psychiatry*, 43, pp. 114–124.

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).

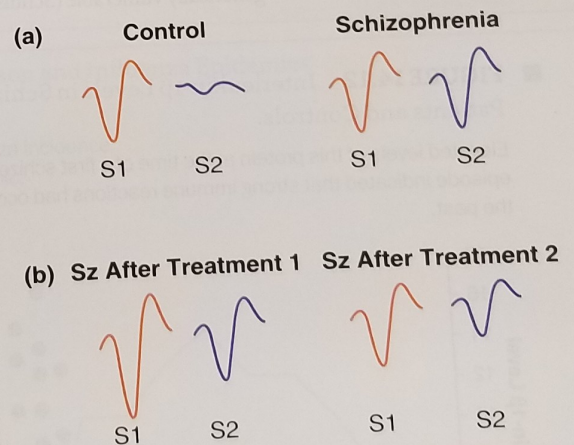
■ **FIGURE 14.10** Brain Activation During Visual and Auditory Hallucinations in a Patient With Schizophrenia.



Source: From “A Functional Neuroanatomy of Hallucinations in Schizophrenia,” by D. A. Silbersweig et al., *Nature*, 378, pp. 176–179. Reprinted by permission of Nature, copyright 1995.

■ **FIGURE 14.11** Absence of P50 Gating in Schizophrenia.

Two clicks are presented 500 milliseconds apart; healthy control subjects show a reduced P50 EEG wave to the second click, a sign of gating (a, left), but those with schizophrenia do not (a, right). After several drug treatments that decrease schizophrenia symptoms, the gating improves (b).



Source: Figure 1 from “Translational utility of rodent hippocampal auditory gating in schizophrenia research: a review and evaluation,” by J. Smucny, K. E. Stevens, A. Olincy, & J. R. Tregellas, 2015, *Translational Psychiatry*, 5, pp. e587.

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

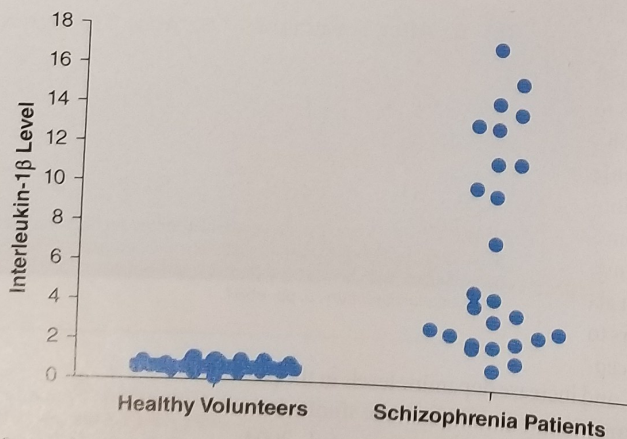
An obvious potential cause of brain defects would be head injury. Several studies have reported an association between schizophrenia and brain damage that occurred within a few years prior to diagnosis (reviewed in David & Prince, 2005). However, the studies have been criticized for several methodological 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-HT_{2A} 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).

FIGURE 14.12 Interleukin-1 β Levels in Schizophrenia Patients and Controls.

Elevated levels of this protein at the time of a first schizophrenic episode indicated that strong immune reactions had occurred in the past.



Source: From "Activation of Brain Interleukin-1 β in Schizophrenia," by J. Söderlund et al., 2009, *Molecular Psychiatry*, 14, pp. 1069–1071. Copyright © 2009 Nature Publishing Group. Used with permission.

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, Tilleskjoer, & 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-1 β 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_{2A} receptors and downregulates mGlu₂ 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).

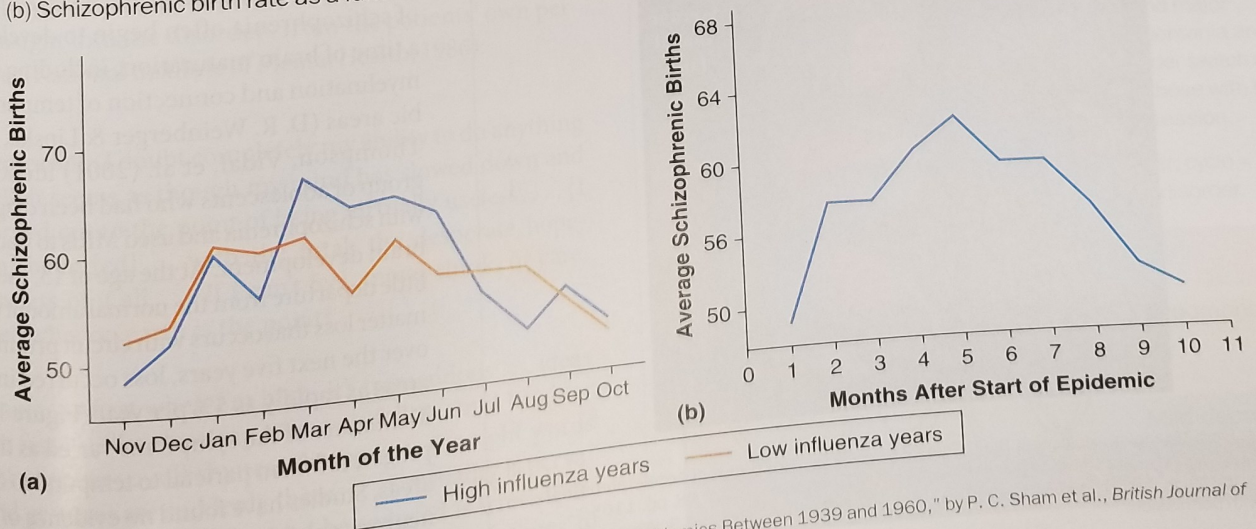
Most of the environmental influences we have been discussing occur during pregnancy or birth; one, however, relates to the father. There is a greater risk of schizophrenia if the father's age at the time of conception exceeds 25, and by paternal age of 50 the risk has increased by two thirds (B. Miller 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 the deeper

FIGURE 14.13 Relationship of Schizophrenic Births to Season and Influenza Epidemics in England and Wales (1939–1960).

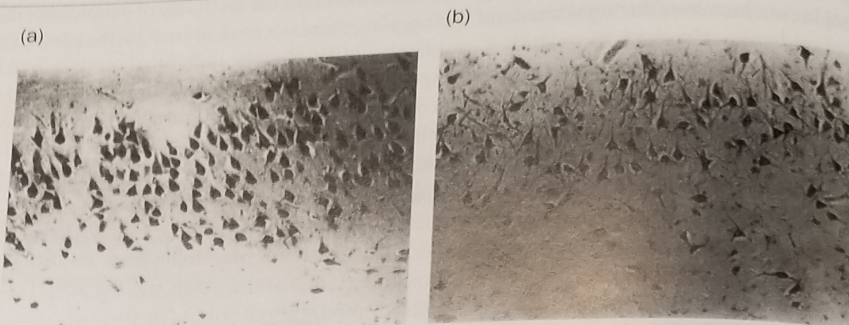
- (a) Schizophrenic birth rates by month during years of high and low influenza incidence.
 (b) Schizophrenic birth rate as a function of time from beginning of epidemic.



Source: From "Schizophrenia Following Pre-natal Exposure to Influenza Epidemics Between 1939 and 1960," by P. C. Sham et al., *British Journal of Psychiatry*, 160, pp. 461–466. Copyright 1992. Reprinted with permission of the publisher.

FIGURE 14.14
Neural Disorganization
in Schizophrenia.

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).



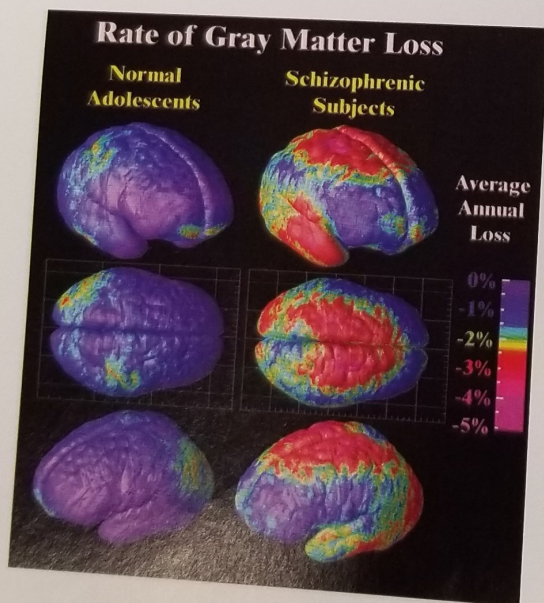
Source: © Arne Scheibel, UCLA.

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, & McMenemy, 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).

FIGURE 14.15 Gray Matter Loss in Schizophrenic Adolescents.

There is some loss in the brains of normal adolescents due to circuit pruning, but the rate of loss is much greater in schizophrenic adolescents. Red and pink areas represent 3%–5% losses annually.



Source: From "Mapping Adolescent Brain Change Reveals Dynamic Wave of Accelerated Gray Matter Loss in Very Early Onset Schizophrenia," by P. M. Thompson, *PNAS*, 98, pp. 11650–11655, fig. 1A, p. 11651, and fig. 5, p. 11653. © 2001 National Academy of Sciences, U.S.A. Used with permission.

Gray matter deficit and ventricular enlargement are ordinarily present at the time of patients' diagnosis (Degreef 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 *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 leads 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] haunt[ed] . . . 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?

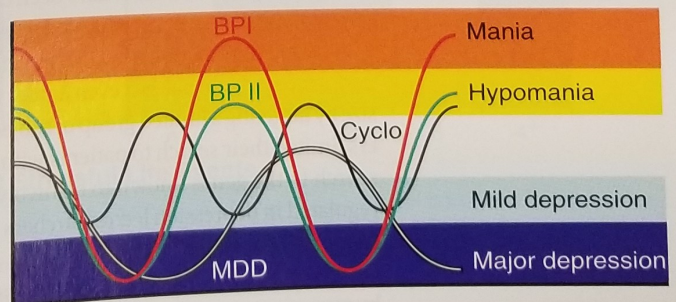
Mania: At first when I'm high, it's tremendous . . . ideas are fast . . . like shooting stars you follow until brighter ones appear . . . all shyness disappears, the right words and gestures are suddenly there. . . . Sensuality is pervasive, the desire to seduce and be seduced is irresistible. Your marrow is infused with unbelievable feelings of ease, power, well-being, omnipotence, euphoria . . . you can do anything . . . but, somewhere this changes.

? What are the affective disorders?

■ FIGURE 14.16 Major Categories of Affective Disorders.

Individuals with BPI alternate between mania and major depression, those with BP II between milder hypomania and major depression, those with Cyclothymic disorder switch rapidly between hypomania and mild depression, and those with MDD alternate between normal mood and major depression.

BP I = bipolar I disorder; BP II = bipolar II disorder; cyclo = cyclothymic disorder; MDD = major depressive disorder.



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, Stiffler, 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% (Kieseppä, 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

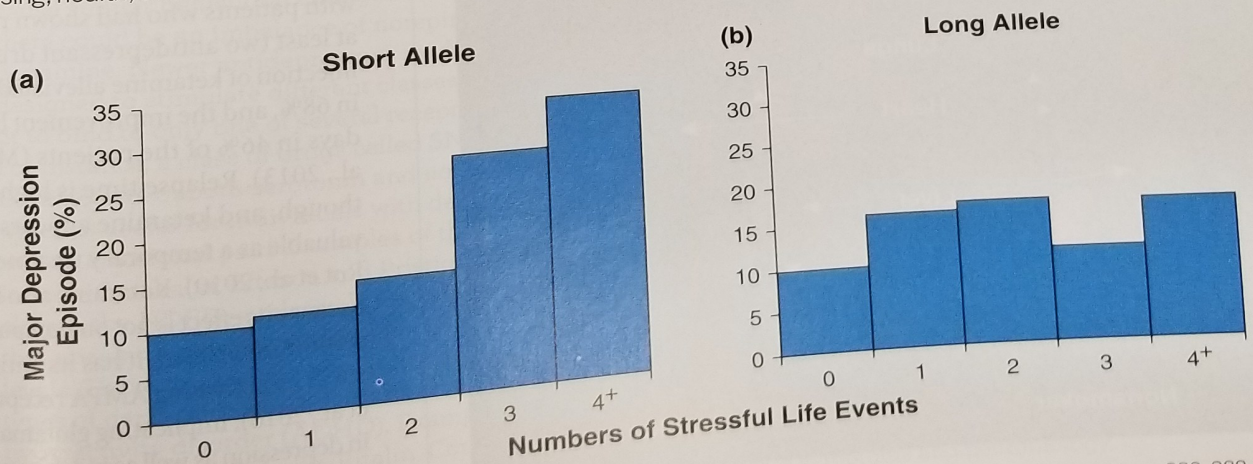
The first effective treatment for depression was discovered accidentally, and theory again followed practice rather than the other way around. *Iproniazid* was introduced as a treatment for tuberculosis, but it was soon discovered that the drug produced elevation of mood (Crane, 1957) and was an effective 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



What is the monoamine hypothesis?

■ **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.



Source: From "Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene," by A. Caspi et al., *Science*, 301, pp. 386–389, fig. 3, p. 389. © 2003. Reprinted by permission of AAAS.

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,

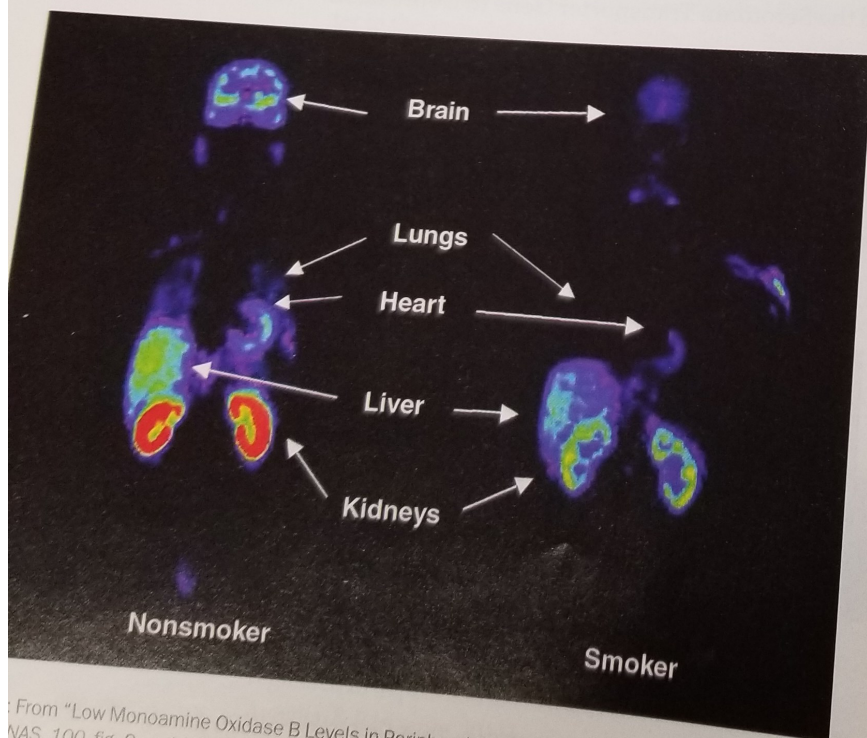
reread the section on nicotine in Chapter 5. Figure 14.18 is a dramatic demonstration of the extensive effect of smoking on monoamine oxidase inhibitor levels throughout the body.

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

FIGURE 14.18 Monoamine Oxidase Levels in the Body of a Nonsmoker and a Smoker.

PET scans were done using a radioactive tracer that binds to monoamine oxidase B. Levels were reduced 33%–46% in smokers. Monoamine oxidase reduction can have beneficial, detrimental, or neutral effects, depending on the location and other conditions.



From "Low Monoamine Oxidase B Levels in Peripheral Organs of Smokers," by J. S. Fowler et al., *Journal of the National Academy of Sciences*, 100, fig. 2, p. 11602. © 2003 National Academy of Sciences, U.S.A. Used with permission.

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 anti-depressants, 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



Source: iStock/BCFC.

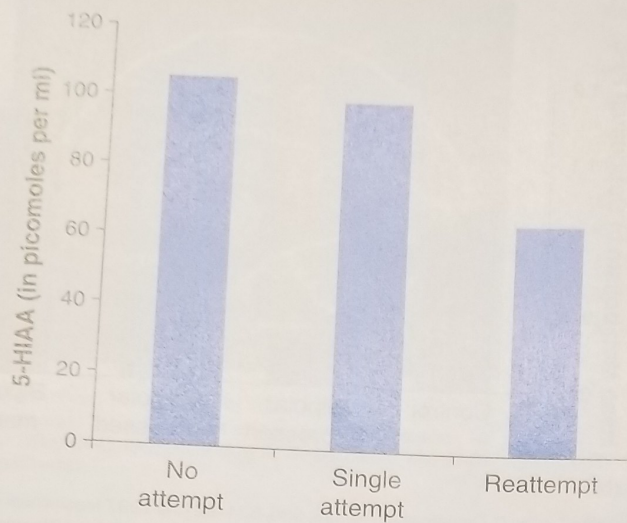
As we have already mentioned, the most prescribed class of antidepressant medications today is the selective serotonin reuptake inhibitors (SSRIs). Although mood disorders are most commonly linked to serotonin (5-HT), abnormal function of other receptors and neurotransmitters can cause similar behavioral 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-HT_{2A} 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.

FIGURE 14.27 Serotonin Levels and Suicide.

Serotonin level, as assessed by the metabolite 5-HIAA, was lower in depressed patients who attempted suicide than in those who did not, and even lower in those who reattempted.



Source: Based on data from Roy, DeJong, and Linnoila (1989).

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 mea-

sures 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.

Heredit

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,

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.

Zai, & Richter, 2004; Hettema, Neale, & Kendler, 2001). 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.).

? What causes anxiety disorders?

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

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What causes anxiety disorders?

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. Marczyński and Urbancic (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' non-combat 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 orbito-

frontal 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 *saliency 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

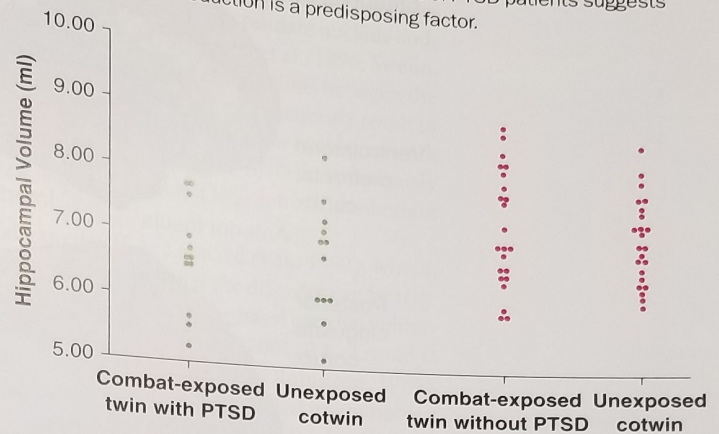
- What neurotransmitter deviations are involved in anxiety disorders?
- What brain anomalies are associated with anxiety disorders?
- What are the environmental, physiological, and genetic contributors to PTSD?

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

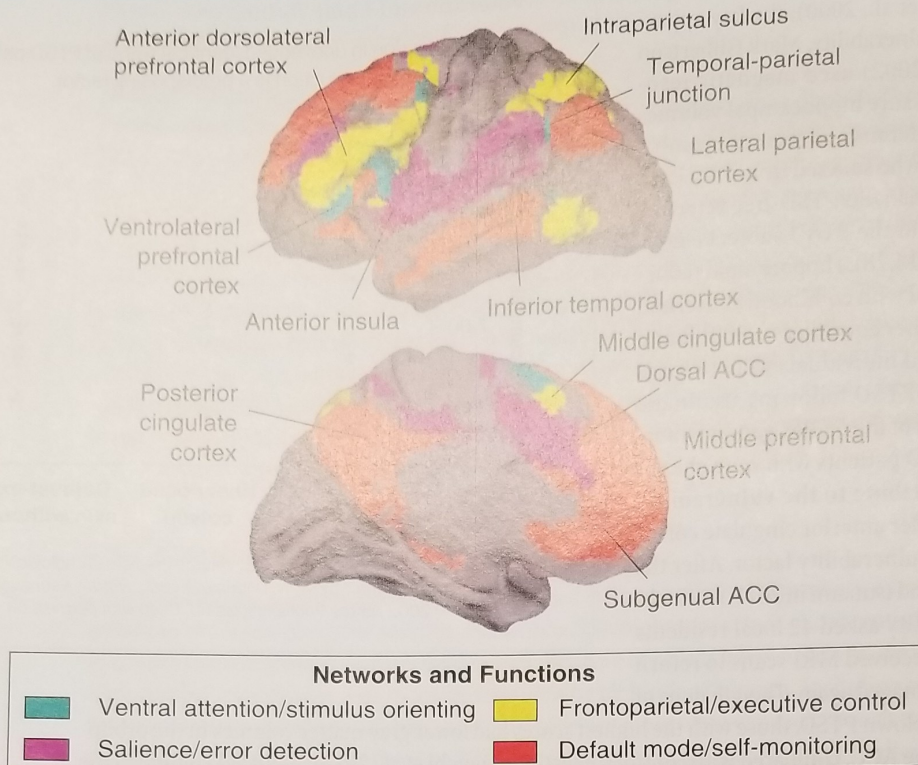
FIGURE 14.28 Hippocampal Volume Is Reduced in Combat Veterans and Their Twins.

Similar reduction in unexposed identical twins of PTSD patients suggests that hippocampal reduction is a predisposing factor.



Source: From "Smaller Hippocampal Volume Predicts Pathologic Vulnerability to Psychological Trauma," by M. W. Gilbertson et al., *Nature Neuroscience*, 5, pp. 1242–1247. Copyright © 2002 Nature Publishing Group. Used with permission.

■ FIGURE 14.29 Networks Involved in Anxiety.



Source: From "Functional Network Dysfunction in Anxiety and Anxiety Disorders," by C. Sylvester et al., 2012, *Trends in Neuroscience*, 35(9). With permission from Elsevier.

will concentrate on two types: obsessive-compulsive disorder and related disorders, and borderline personality disorder.



What is obsessive-compulsive disorder, and what causes it?

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

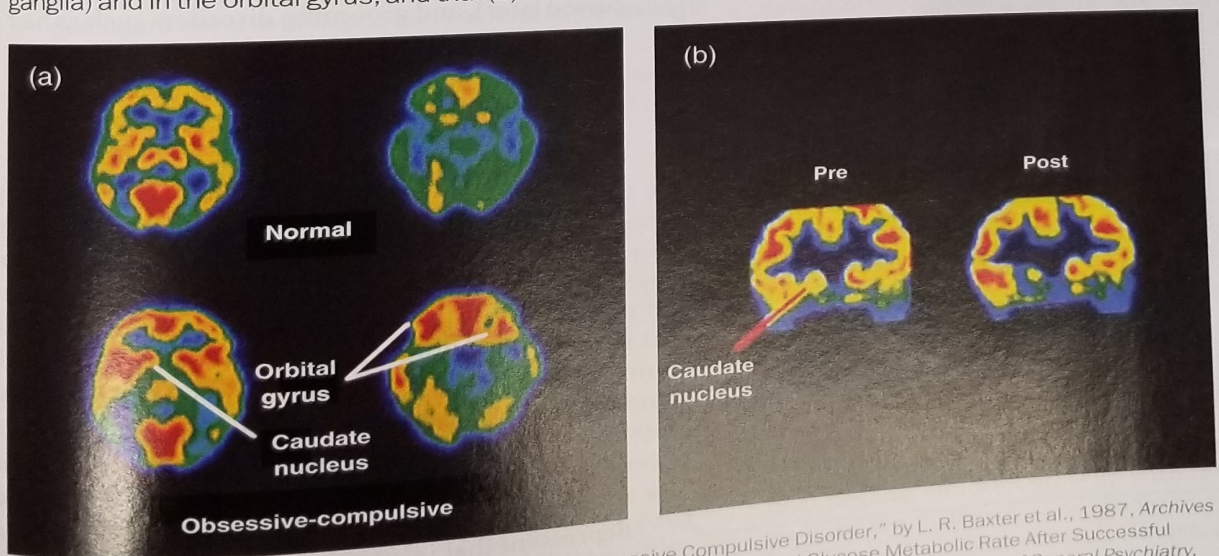
organizing that someone with OCD would experience. Instead, those feelings of perfection are perceived to be occasional and reasonable. OCPD is much harder to treat, compared to OCD.

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 associated with symptoms of OCD, such as worry. However, both drug treatment and behavior increases associated with symptoms of OCD, such as 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; Szeszko 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.

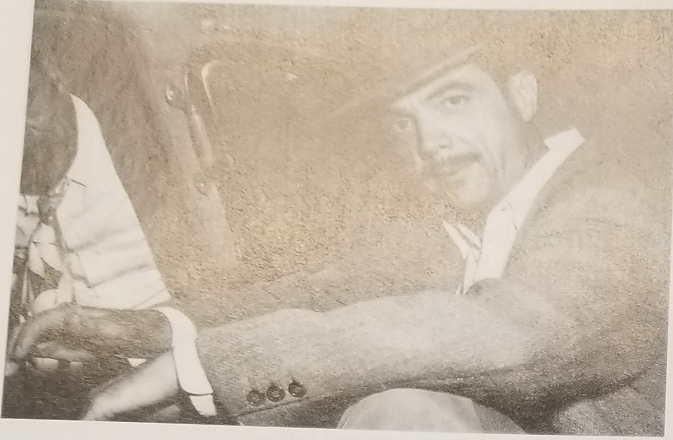
Scans of OCD patients show that (a) activity is elevated in the caudate nucleus (a part of the basal ganglia) and in the orbital gyrus, and that (b) behavior therapy reduces this activity in the caudate nucleus.



Sources: (a) From “Local Cerebral Glucose Metabolic Rates in Obsessive Compulsive Disorder,” by L. R. Baxter et al., 1987, *Archives of General Psychiatry*, 44(14), pp. 211–218. (b) From “Systematic Changes in Cerebral Glucose Metabolic Rate After Successful Behavior Modification Treatment of Obsessive-Compulsive Disorder,” by J. M. Schwartz et al., 1996, *Archives of General Psychiatry*, 53(14), pp. 109–113.

FIGURE 14.31 Howard Hughes.

Hughes was an extraordinarily successful businessman and dashing man-about-Hollywood, but he spent his later years crippled by symptoms of OCD. His life was documented in the Warner Brothers film *The Aviator*.



Source: Bettmann/Getty Images.

FIGURE 14.32 Excessive Grooming and the *Sapap3* Gene.

The mouse lacking the *Sapap3* gene (top) has groomed to the point of creating lesions on the neck and face and even damaging the eye.



Source: Courtesy of Jing Lu, Jeff Welch, and Guoping Feng.

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



Searchers climb over debris piled almost to the ceiling in the Collyer home.

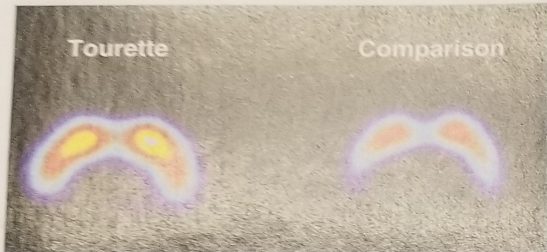
Source: *New York Daily News*/Contributor/*New York Daily News*/Getty Images.

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).

FIGURE 14.33 Increased Dopamine Activity in the Caudate Nuclei in Tourette Syndrome.

These two scans have not been superimposed over images of a brain; you can refer to Figure 14.30b to see where the caudate nuclei are located in the brain.



Source: From "[123I]α-CIT SPECT Imaging of Striatal Dopamine Transporter Binding in Tourette's Disorder," by R. T. Malison et al., 1995, *American Journal of Psychiatry*, 152, pp. 1359–1361. Copyright © 1995 American Psychiatric Publishing. Used with permission.

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 people's 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 alley-way 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.

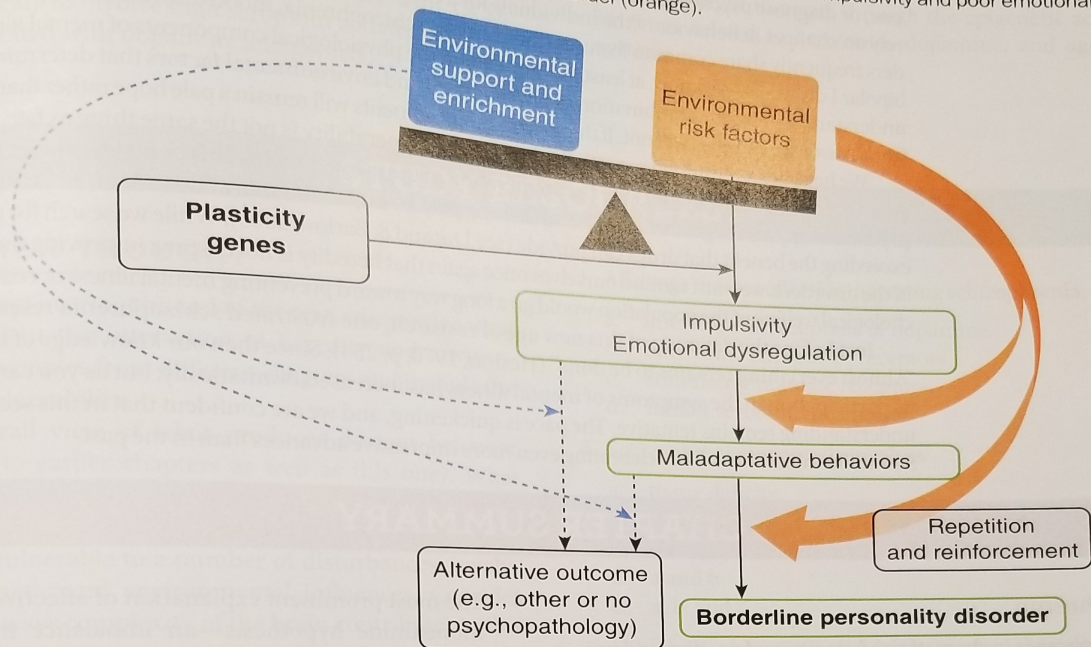
Tourette syndrome, like OCD, involves increased activity in the basal ganglia. But unlike OCD, the most frequently prescribed drug for Tourette is an antidopaminergic drug, haloperidol, though newer antidopamine drugs are also being used. One effect dopamine has is motor activation, and Malison and his 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.

FIGURE 14.34 Integrative Model of Borderline Personality Disorder.

Although environmental support can prevent the imbalances that result in epigenetic changes to plasticity genes resulting in borderline personality disorder (blue), poor environmental features turn on genes that result in impulsivity and poor emotional control, which leads to the poor behavioral choices characteristic of the disorder (orange).



Source: Figure 2 from "Genetics of borderline personality disorder: systematic review and proposal of an integrative model," by A. Amad et al., 2014, *Neuroscience and Biobehavioral Reviews*, 40, pp. 6–19. Copyright © 2014 Elsevier. Used with permission.

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 5HTTLPR, dopamine transporters such as DAT1, and enzymes that make 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 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