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Course of Study: **Introduction to Biological Psychology**

Course Code: **PSYC10009**

Name of Designated Person undertaking scanning: **Pete Barrett**

Title of Book Chapter: **Abnormal Behaviour**

Author(s)/Editor(s) of Book Chapter: **James W. Kalat**

Title of Book: **Biological Psychology**

Author/Editor of Book: **James W. Kalat**

Pages: **445 - 470**

Publisher and Date of Publication: **Wadsworth / Cengage Learning, 2013**

Place of Publication: **Stamford, CT; Andover**

Abnormal Behavior

CHAPTER OUTLINE

MODULE 15.1 Mood Disorders

Major Depressive Disorder
Antidepressant Drugs
Bipolar Disorder
Seasonal Affective Disorder
In Closing: Biology of Mood Swings

MODULE 15.2 Schizophrenia

Diagnosis
Genetics
The Neurodevelopmental Hypothesis
Treatments
In Closing: Many Remaining Mysteries
Interactive Exploration and Study

MAIN IDEAS

1. Psychological disorders result from a combination of environmental and biological influences, including genetics.
2. The effectiveness of certain drugs provides a clue as to the underlying basis of depression and schizophrenia, but many questions remain about how these drugs exert their effects.
3. Schizophrenia may be the result of genetic or other problems that impair early development of the brain.

Are mental illnesses really *illnesses*, analogous to tuberculosis or influenza? Or are they normal reactions to abnormal experiences? They are not exactly either. They are outcomes that combine biological predispositions with experiences. To control them, we need a good understanding of both aspects.

Abnormal behavior comes in many varieties. *The Diagnostic and Statistical Manual of Mental Disorders, fourth edition* (American Psychiatric Association, 1994) lists hundreds of disorders. This chapter deals with mood disorders—depression and bipolar disorder—and schizophrenia. These disorders have been the focus of a huge amount of biological research. Chapter 12 discussed anxiety disorders and Chapter 3 had a section about addictions.

OPPOSITE: PET scans show the brain areas that increase their activation during visual and auditory hallucinations by a patient with schizophrenia.



MODULE 15.1

Mood Disorders

Different people can get to the same place by different routes. For example, the people in a room at any moment may have started from different cities or different parts of a city and traveled in different ways, although they all reached the same destination. Similarly, people can become depressed through different routes, including genetics, traumatic experiences, hormonal problems, substance abuse, head injuries, brain tumors, and other illnesses. Despite having different causes, or combinations of causes, these people all look and act depressed (Figure 15.1). In this module, we explore some of the many factors that contribute to depression.

I Major Depressive Disorder

Many people say they feel “depressed” when they feel sad or discouraged. Major depression is much more intense and prolonged. According to the *DSM-IV* (American Psychiatric Association, 1994), people with a **major depression** feel sad and helpless every day for weeks at a time. They have little energy, feel worthless, contemplate suicide, have trouble sleeping, cannot concentrate, find little pleasure, and can hardly even imagine being happy again.

Absence of happiness is a more reliable symptom than increased sadness. In one study, people carried a beeper that sounded at unpredictable times to signal them to describe their emotional reactions at the moment. People with depression reported only an average number of unpleasant experiences but far below the average number of pleasant ones (Peters, Nicolson, Berkhof, Delespaul, & deVries, 2003). In other studies, people examined photographs or films as researchers recorded their reactions. Individuals with depression reacted normally to sad or frightening depictions but seldom smiled at the comedies or pleasant pictures (Rotenberg, Kasch, Gross, & Gotlib, 2002; Sloan, Strauss, & Wisner, 2001). Additional studies found that people with depression show a decreased response to happy facial expressions (Monk et al., 2008) and a decreased response to a likely reward (McFarland & Klein, 2009).

A survey reported that about 5% of adults in the United States have a “clinically significant” depression (i.e., serious

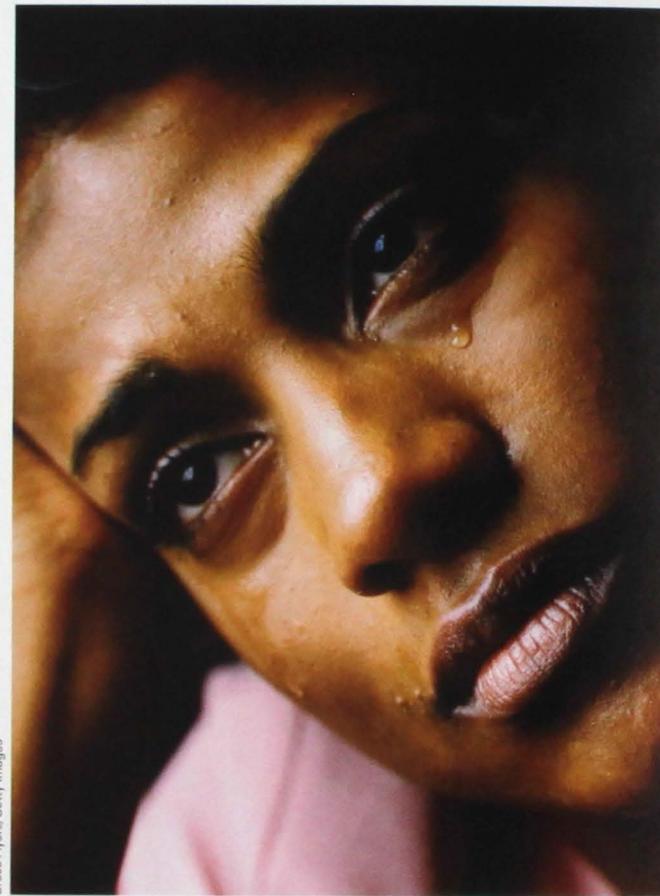


FIGURE 15.1 The face of depression

Depression shows in a person's face, walk, voice, and mannerisms.

enough to warrant attention) within a given year, and more than 10% do at some point in life (Narrow, Rae, Robins, & Regier, 2002). Reported one-year prevalence rates vary among countries and ethnic groups, from less than 5% among Chinese-Canadians to more than 15% in India (Murali, 2001; Tiwari & Wang, 2006). It is hard to know how seriously to take these numbers. Standards for diagnosis inevitably vary from place to place, and psychiatrists have no laboratory tests to confirm a diagnosis.

Childhood depression is about equally common for boys and girls, but beyond about age 14, depression is more common in females (Twenge & Nolen-Hoeksema, 2002). Various hypotheses have been advanced to explain this tendency, but none is well established.

Although some people suffer from long-term depression (Klein, 2010), it is more common to have episodes of depression separated by periods of normal mood. The first episode is special in certain regards. The first episode is generally longer than most of the later ones, and most patients can identify a highly stressful event that triggered the first episode. For later episodes, people are less and less likely to identify a triggering event (Post, 1992). It is as if the brain learns how to be depressed and gets better at it (Monroe & Harkness, 2005). In that regard it is like epilepsy and migraine headaches: The more often you have had an episode, the easier it is to start another one (Post & Silberstein, 1994).

Genetics

Studies of twins and adopted children indicate a moderate degree of heritability for depression (Shih, Belmonte, & Zandi, 2004). However, although researchers have identified several genes linked to depression, none of the genes by itself has a large effect (Camp et al., 2005; Holmans et al., 2007).

One reason why no gene shows a strong link to depression is that when we talk about depression, we are probably lumping together at least two distinguishable syndromes. People with early-onset depression (before age 30) have a high probability of other relatives with depression (Bierut et al., 1999; Kendler, Gardner, & Prescott, 1999; Lyons et al., 1998), as well as relatives with anxiety disorders, attention-deficit disorder, alcohol or marijuana abuse, obsessive-compulsive disorder, bulimia, migraine headaches, and irritable bowel syndrome (Q. Fu et al., 2002; Hudson et al., 2003). People with late-onset depression (especially after age 45 to 50) have a high probability of relatives with circulatory problems (Kendler, Fiske, Gardner, & Gatz, 2009). Distinguishing between early-onset and late-onset cases may lead to progress in identifying genes, and perhaps in selecting effective therapies.

Still, given the difficulty so far in identifying any gene strongly linked to depression, another hypothesis arose: Perhaps the effect of a gene varies with the environment. One gene controls the serotonin transporter, a protein that regulates the ability of axons to reabsorb serotonin after its release, to recycle it for further use. Investigators examined the serotonin transporter genes of 847 young adults, identifying two types: the “short” type and the “long” type. They also asked each participant to report certain stressful events over five years, including financial setbacks, loss of job, divorce, and so forth. Figure 15.2 shows the results. For people with two short forms of the gene, increasing numbers of stressful experiences led to a big increase in the probabil-

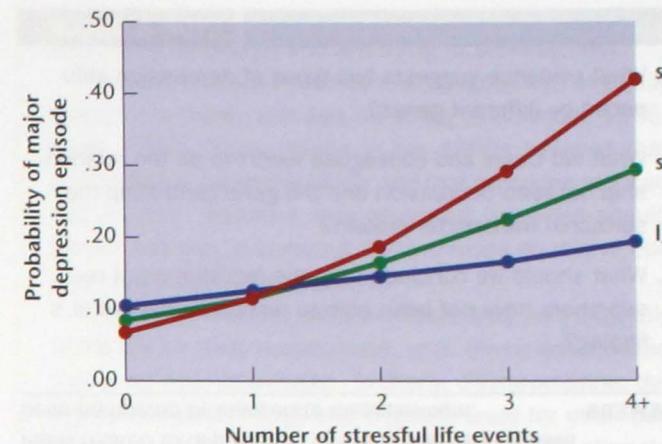


FIGURE 15.2 Genetics, stress, and depression

The effect of the serotonin transporter gene depends on the amount of stress. (Reprinted by permission from A. Caspi, et al., “Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene,” *Science*, 301, pp. 386–389. © 2003 AAAS.)

ity of depression. For those with two long forms, stressful events only slightly increased the risk of depression. Those with one short and one long gene were intermediate. In other words, the short form of the gene by itself did not lead to depression, but it might magnify the reaction to stressful events (Caspi et al., 2003).

This report provoked a great deal of excitement. However, since then most researchers have failed to replicate the result, finding no significant relationship between depression and the serotonin transporter gene itself and no interaction between effects of the gene and stress (Munafo, Durrant, Lewis, & Flint, 2009; Risch et al., 2009).

When a result in psychology, medicine, or any other field cannot be replicated, the obvious interpretation is that the first report was wrong. Given the huge number of researchers collecting studies, occasionally a random fluctuation in data suggests a relationship between variables that are in fact unrelated. However, here is another possibility: If a study finds no significant correlation between two variables, perhaps one or both of the variables was poorly measured. (We can't expect a poorly measured variable to correlate with anything else.) Our measurements of depression are probably good enough, but the measurements of stress are more doubtful. Generally researchers ask people how many stressful events they have experienced, and simply count them. Losing a job can be extremely stressful or hardly stressful at all, depending on how easily someone found an equal or better job. Similarly, divorce is much more stressful to some people than others. Also, the biochemical methods used to measure short vs. long forms of the gene have been inaccurate in many cases (Wray et al., 2009). We should await more research with more careful measurements before we draw a firm conclusion.

STOP & CHECK

- What evidence suggests two types of depression influenced by different genes?
- What did Caspi and colleagues report to be the relationship between depression and the gene controlling the serotonin transporter protein?
- What should we conclude from the fact that most researchers have not been able to replicate Caspi et al.'s finding?

ANSWERS

been hampered by inaccurate measurement.
really related to depression, or the studies so far have
not increased. **3.** Either variation in this gene is not
absence of stressful experiences, their probability is
experiences by becoming depressed. However, in the
are more likely than other people to react to stress
problems. **2.** People with the short form of the gene
depression have a high probability of circulatory
logical disorders. Relatives of people with late-onset
have a high risk of depression and many other psychi-
1. Relatives of people with early-onset depression

Other Biological Influences

Genetic differences partly explain why some people are more vulnerable to depression than others are, but other factors contribute also. A few cases of depression are linked to viral infections. Borna disease, a viral infection of farm animals, produces periods of frantic activity alternating with periods of inactivity (Figure 15.3). In 1985, investigators tested 370 people for possible exposure to this virus (Amsterdam et al.,

1985). Only 12 people tested positive for Borna disease virus, but all 12 were suffering from major depression or bipolar disorder. These 12 were a small percentage of the 265 depressed people tested; still, none of the 105 nondepressed people had the virus.

Since then, thousands of people have been tested in Europe, Asia, and North America. The Borna virus is found in about 5% of normal people and about one-third of people with severe depression or schizophrenia (Bode, Ferszt, & Czech, 1993; Bode, Riegel, Lange, & Ludwig, 1992; Nunes et al., 2008; Terayama et al., 2003). The role of this virus in psychiatric disorders remains uncertain, but the results so far suggest that viruses might be a predisposing factor in some cases.

Hormones may be another trigger for depression. Stress is accepted as an important factor in depression, and stress increases release of cortisol, as discussed in Chapter 12. About 20% of women report some degree of **postpartum depression**—that is, depression after giving birth—and many researchers suspect that hormonal fluctuations are a contributing factor. Stress hormones reach a peak late in pregnancy, and ovarian hormones go through major changes around the time of delivery. One study found that after a drug-induced drop in estradiol and progesterone levels, women with a history of postpartum depression suddenly show new symptoms of depression, whereas other women do not (M. Bloch et al., 2000). Among older men, a declining level of the hormone testosterone is associated with increased probability of depression (Almeida, Yeap, Hankey, Jamrozik, & Flicker, 2008). However, few studies have been done that directly link hormones to depression, and the relationship remains uncertain (Brummelte & Galea, 2010). We do know that the risk of postpartum depression increases in women with previous bouts of depression.

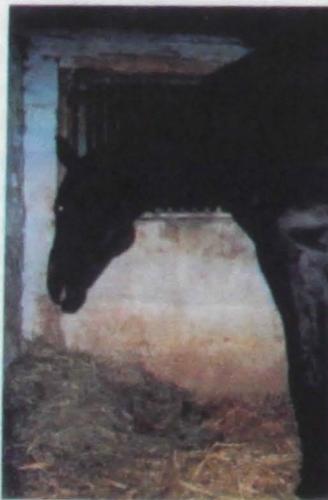


FIGURE 15.3 Symptoms of Borna disease

Animals infected with Borna disease have periods of frantic activity alternating with inactivity, much like a person with bipolar disorder. (left) Horse with Borna disease. (right) Same horse after recovery. (Figure 2, page 174, from Bode L. and Ludwig H., (1997). "Clinical similarities and close genetic relationship of human and animal Borna disease virus." Archives of Virology (Supplement 13), 167–182. Springer-Verlag. Photo scan by Kevin J. Nolte.)

sion, stressful life events, and a lack of social support—that is, the same factors linked to major depression at any other time of life (O'Hara, 2009).

Abnormalities of Hemispheric Dominance

Studies of normal people have found a fairly strong relationship between happy mood and increased activity in the left prefrontal cortex (Jacobs & Snyder, 1996). Most people with depression have decreased activity in the left and increased activity in the right prefrontal cortex, and this imbalance is stable over years despite changes in symptoms of depression (Davidson, 1984; Pizzagalli et al., 2002; Vuga et al., 2006). Here's something you can try: Ask someone to solve a cognitive problem, such as, "See how many words you can think of that start with *hu-*" or "Try to remember all the ingredients you've ever seen on a pizza." Then unobtrusively watch the person's eye movements to see whether they gaze right or left. Most people gaze to the right during verbal tasks, but most individuals with depression gaze to the left, suggesting right-hemisphere dominance (Lenhart & Katkin, 1986).

TRY IT YOURSELF

- Some people offer to train you to use the right hemisphere of your brain more strongly, allegedly to increase creativity. If they were successful, can you see any disadvantage?

ANSWER

Increased tendency toward depression.
4. People with predominant right-hemisphere activity show an increased tendency toward depression.

I Antidepressant Drugs

You might assume that investigators first determine the causes of a psychological disorder and then develop medications based on the causes. The opposite order has been more common: First investigators find a drug that seems helpful, and then they try to figure out how it works. Like many other psychiatric drugs, the early antidepressants were discovered by accident.

APPLICATIONS AND EXTENSIONS**Accidental Discoveries of Psychiatric Drugs**

Nearly all of the earliest psychiatric drugs were discovered by accident. Disulfiram, for example, was originally used in the manufacture of rubber. Someone noticed that workers in a certain rubber factory avoided alcohol and traced the cause to disulfiram, which had altered the workers' metabolism so they became ill after drinking al-

cohol. Disulfiram became the drug Antabuse, sometimes prescribed for people who are trying to avoid alcohol.

The use of bromides to control epilepsy was originally based on a theory that was all wrong (Friedlander, 1986; Levitt, 1975). Many people in the 1800s believed that masturbation caused epilepsy and that bromides reduced sexual drive. Therefore, they reasoned, bromides should reduce epilepsy. It turns out that bromides do relieve epilepsy but for different reasons.

Iproniazid, the first antidepressant drug, was originally marketed to treat tuberculosis, until physicians noticed that it relieved depression. Similarly, chlorpromazine, the first antipsychotic drug, was originally used for other purposes, until physicians noticed its ability to alleviate schizophrenia. For decades, researchers sought new drugs entirely by trial and error. Today, researchers evaluate new potential drugs in test tubes or tissue samples until they find one with a potential for stronger or more specific effects on neurotransmission. The result is the use of fewer laboratory animals. ■

Types of Antidepressants

Antidepressant drugs fall into several categories, including tricyclics, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and atypical antidepressants (Figure 15.4). The **tricyclics** (e.g., imipramine, trade name Tofranil) operate by blocking the transporter proteins that reabsorb serotonin, dopamine, and norepinephrine into the presynaptic neuron after their release. The result is to prolong the presence of the neurotransmitters in the synaptic cleft, where they continue stimulating the postsynaptic cell. However, the tricyclics also block histamine receptors, acetylcholine receptors, and certain



FIGURE 15.4 Antidepressant pills

Tricyclic drugs block the reuptake of catecholamines and serotonin by presynaptic terminals. Selective serotonin reuptake inhibitors, such as Prozac, have similar effects but are limited to serotonin. MAOIs block an enzyme that breaks down catecholamines and serotonin.

sodium channels (Horst & Preskorn, 1998). As mentioned in Chapter 9, blocking histamine produces drowsiness. Blocking acetylcholine leads to dry mouth and difficulty urinating. Blocking sodium channels causes heart irregularities, among other problems. People have to limit their use of tricyclic drugs to minimize these side effects.

The **selective serotonin reuptake inhibitors (SSRIs)** are similar to tricyclics but specific to the neurotransmitter serotonin. For example, fluoxetine (trade name Prozac) blocks the reuptake of serotonin. SSRIs produce milder side effects than the tricyclics, but their effectiveness is about the same. Other common SSRIs include sertraline (Zoloft), fluvoxamine (Luvox), citalopram (Celexa), and paroxetine (Paxil or Seroxat). Several newer drugs are **serotonin norepinephrine reuptake inhibitors (SNRIs)**, such as duloxetine (Cymbalta) and venlafaxine (Effexor). As you might guess, they block reuptake of serotonin and norepinephrine.

The **monoamine oxidase inhibitors (MAOIs)** (e.g., phenelzine, trade name Nardil) block the enzyme monoamine oxidase (MAO), a presynaptic terminal enzyme that metabolizes catecholamines and serotonin into inactive forms. When MAOIs block this enzyme, the presynaptic terminal has more of its transmitter available for release. Generally, physicians prescribe tricyclics or SSRIs first and then try MAOIs with people who did not respond to the other drugs (Thase, Trivedi, & Rush, 1995). People taking MAOIs must avoid foods containing tyramine—including cheese, raisins, and many others—because a combination of tyramine and MAOIs increases blood pressure. Figure 15.5 summarizes the mechanisms of tricyclics, SSRIs, and MAOIs.

The **atypical antidepressants** are a miscellaneous group—everything other than the types just discussed (Horst & Preskorn, 1998). One example is bupropion (Wellbutrin), which inhibits reuptake of dopamine and to some extent norepinephrine but not serotonin.

In addition, many people use St. John's wort, an herb. Because it is marketed as a nutritional supplement instead of a drug, the U.S. Food and Drug Administration does not regulate it, and its purity varies from one bottle to another. It has the advantage of being less expensive than antidepressant drugs. An advantage or disadvantage, depending on your point of view, is that it is available without prescription. People can get it easily but often take inappropriate amounts. Its effectiveness appears to be about the same as that of standard antidepressant drugs (Kasper, Caraci, Forti, Drago, & Aguglia, 2010). However, it has a potentially dangerous side effect: All mammals have a liver enzyme that breaks down plant toxins. St. John's wort increases the effectiveness of that enzyme. Increasing the breakdown of toxins sounds like a good thing, but the enzyme also breaks down most medicines. Therefore,

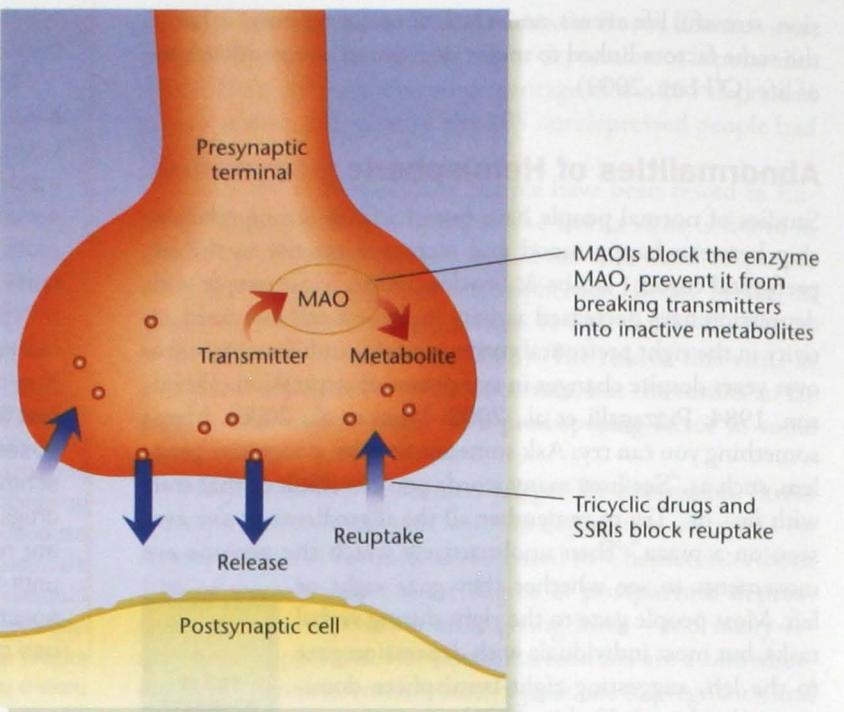


FIGURE 15.5 Routes of action of antidepressants

Tricyclics block the reuptake of dopamine, norepinephrine, and serotonin. SSRIs specifically block the reuptake of serotonin. SNRIs block reuptake of serotonin and norepinephrine. MAOIs block the enzyme MAO, which converts dopamine, norepinephrine, or serotonin into inactive chemicals. (© Cengage Learning 2013)

taking St. John's wort decreases the effectiveness of other drugs you might be taking—including other antidepressant drugs, cancer drugs, and AIDS drugs (He, Yang, Li, Du, & Zhou, 2010; Moore et al., 2000).

STOP & CHECK

5. What are the effects of tricyclic drugs?

6. What are the effects of SSRIs?

7. What are the effects of MAOIs?

ANSWERS

5. Tricyclic drugs block reuptake of serotonin and catecholamines. They also block histamine receptors, acetylcholine receptors, and certain sodium channels, availability of these transmitters.
6. SSRIs selectively inhibit the reuptake of serotonin, thereby producing antidepressant side effects.
7. MAOIs block the enzyme MAO, which breaks down catecholamines and serotonin. The result is increased availability of these transmitters.

How Do Antidepressants Work?

Understanding how antidepressants work should shed some light on the causes of depression. The commonly used antidepressants increase the presence of serotonin or other neurotransmitters at the synapse, and so it might seem that the

problem in depression is too little of the neurotransmitters. However, the story is not that simple. So far as we can tell from blood metabolites, people with depression have approximately normal levels of release of neurotransmitters. In fact, some studies show that people with depression have an *increase* in serotonin release (Barton et al., 2008). Furthermore, it is possible to decrease serotonin levels suddenly by consuming all the amino acids except tryptophan, the precursor to serotonin. For most people, this decrease in serotonin does not provoke any feelings of depression (Neumeister et al., 2004, 2006).

Furthermore, given that different drugs act in different ways on different neurotransmitters, wouldn't you expect some of them to be more effective than others? So far as we can tell, all of them are about equal in effectiveness (Montgomery et al., 2007). Two studies examined patients who failed to respond to an antidepressant drug within a few weeks. In one study the psychiatrists added a second drug, and in the other study they switched patients from one drug to the other. The result was that some patients who did not respond to the first drug did respond after a few weeks on the new regimen (Rush et al., 2006; Trivedi et al., 2006). Should we conclude, as the researchers did, that adding a drug or switching drugs helped? No. Unfortunately, neither study included a control group that stayed on the first drug for the additional time. In short, we have no clear evidence that any antidepressant drug produces any different effects from any other.

The time course of effects poses an additional threat to any explanation in terms of neurotransmitters: Antidepressant drugs produce their effects on neurotransmitters in the synapses within minutes to hours, depending on the drug, but people need to take the drugs for 2 or more weeks before they experience any mood elevation (Stewart et al., 1998). This delay of benefits strongly suggests that increasing the levels of neurotransmitters at synapses does not explain the benefits of the drugs. Perhaps the neurotransmitter effects are not even relevant.

Today, much research attention focuses on neurotrophins. As discussed in Chapter 5, neurotrophins aid in the survival, growth, and connections of neurons. Most people with depression have lower than average levels of a neurotrophin called *brain-derived neurotrophic factor (BDNF)* that is important for synaptic plasticity, learning, and proliferation of new neurons in the hippocampus (Martinowich, Manji, & Lu, 2007; Sen, Duman, & Sanacora, 2008). As a result of low BDNF, most people with depression have a smaller than average hippocampus, impaired learning, and reduced production of new hippocampal neurons. Prolonged use of antidepressant drugs generally increases BDNF production and improves learning and formation of new neurons. This process takes weeks (Drzyzga, Marcinowska, & Obuchowicz, 2009; Vetencourt et al., 2008). That is, the time course for BDNF and changes in the hippocampus matches the time course for behavioral recovery. Procedures that block neuron production also block the behavioral benefits of antidepressant drugs (Airan et al., 2007).

Apparently BDNF by itself does not automatically elevate mood, but it helps by facilitating new learning that builds new synapses and removes many old ones. That mode of action explains why antidepressants help people in depression—who might profit from substituting new thoughts for old ones—but fail to elevate mood for normal people (Castrén & Rantamäki, 2010).

Although this story may seem convincing, the conclusion remains tentative, as a few antidepressant drugs improve mood without demonstrable effects on BDNF (Basterzi et al., 2008; Matrisciano et al., 2009). Perhaps antidepressants work in more than one way.

STOP & CHECK

8. In what way does the time course of antidepressants conflict with the idea that they improve mood by increasing neurotransmitter levels?
9. As opposed to an interpretation in terms of neurotransmitter levels, what is an alternative explanation for the benefits of antidepressant drugs?

ANSWERS

8. Antidepressants produce their effects on serotonin and norepinephrine in the hippocampus, which gradually promotes growth of new neurons, new synapses, and new learning in the hippocampus.
9. Antidepressant drugs gradually increase production of BDNF, and other neurotransmitters quickly, but their behavioral benefits develop gradually over 2 to 3 weeks.

How Effective Are Antidepressants?

So far we have considered explanations of how antidepressants work. How sure are we that they do work? Not everyone is convinced (Kirsch, 2010), and at least we have to say that the effectiveness is limited.

In most cases, depression occurs in episodes. That is, even without treatment, many people recover within a few months. Furthermore, giving someone a medication produces an expectation of improvement, thereby enhancing the probability of recovery, even if the medication itself is ineffective. To test the effectiveness of an antidepressant drug, researchers need to compare its effects to those of a placebo (a pharmacologically inactive substance).

Figure 15.6 summarizes the results of many experiments in which people were randomly assigned to receive antidepressant drugs or placebos. The horizontal axis represents the mean amount of improvement on the Hamilton Depression Rating Scale. The pink triangles represent patients receiving the drug in a study, and the gray circles represent patients receiving a placebo. The size of the triangle or circle is proportional to the number of patients in a group. Many people respond well on placebos, either because of spontaneous recovery over time or because of the expectation that a pill induced. Younger patients are particularly likely

to respond to placebos (Bridge, Birmaher, Iyengar, Barbe, & Brent, 2009). For patients with mild to moderate depression, the results for placebo groups overlap those for drug groups, and the differences between the groups are, on average, too small to be of much clinical significance. Only for people with severe depression do the drugs show a meaningful advantage (Kirsch et al., 2008). Another independent analysis of the research confirmed that the drugs show no clear benefit over placebos for people with mild to moderate depression (Fournier et al., 2010). Furthermore, even at the most severe levels of depression, antidepressants help some people and not others (Uhr et al., 2008).

An alternative to antidepressant drugs is psychotherapy. Reviews of the research literature find that antidepressant drugs and psychotherapy are about equally effective for treating all levels of depression, from mild to severe, with three exceptions: First, the drugs work better for *dysthymia*, a long-term, almost life-long condition of unhappy mood. Nearly all of the research studies examined short-term therapies, and it may be that brief psychotherapy is ineffective for such a long-term condition. Second, antidepressants are generally ineffective for patients who had suffered abuse or neglect during early childhood or patients with multiple psychological disorders. Those patients usually respond better to psychotherapy (Asarnow et al., 2009; Nemeroff et al., 2003). Third, psychotherapy is more likely to have long-

term benefits, reducing the likelihood of a relapse months or years after the end of treatment (Bortolotti, Menchetti, Bellini, Montaguti, & Berardi, 2008; Imel, Malterer, McKay & Wampold, 2008).

Would a combination of antidepressant drugs and psychotherapy work better than either one alone? On average, people who improve while receiving both treatments improve more than people receiving either one alone. However, the percentage of people showing improvement increases only slightly with combined treatment (de Maat et al., 2008; Hollon et al., 2005). That is, it is not the case that many people respond better to one treatment than the other. Evidently, many people with mild to moderate depression improve with only a placebo, another group improves with either antidepressants or psychotherapy, a few respond better to one or the other, and the remainder—one-third to one-half, by most estimates—do not respond well to either one (Friedman et al., 2009; Hollon, Thase, & Markowitz, 2002; Thase et al., 1997).

The effects of antidepressants and those of psychotherapy overlap more than we might have guessed. Brain scans show that antidepressants and psychotherapy increase metabolism in the same brain areas (Brody et al., 2001; S. D. Martin et al., 2001). That similarity should not be terribly surprising if we accept the mind–body monism position. If mental activity is the same thing as brain activity, then changing someone's thoughts should indeed change brain chemistry.

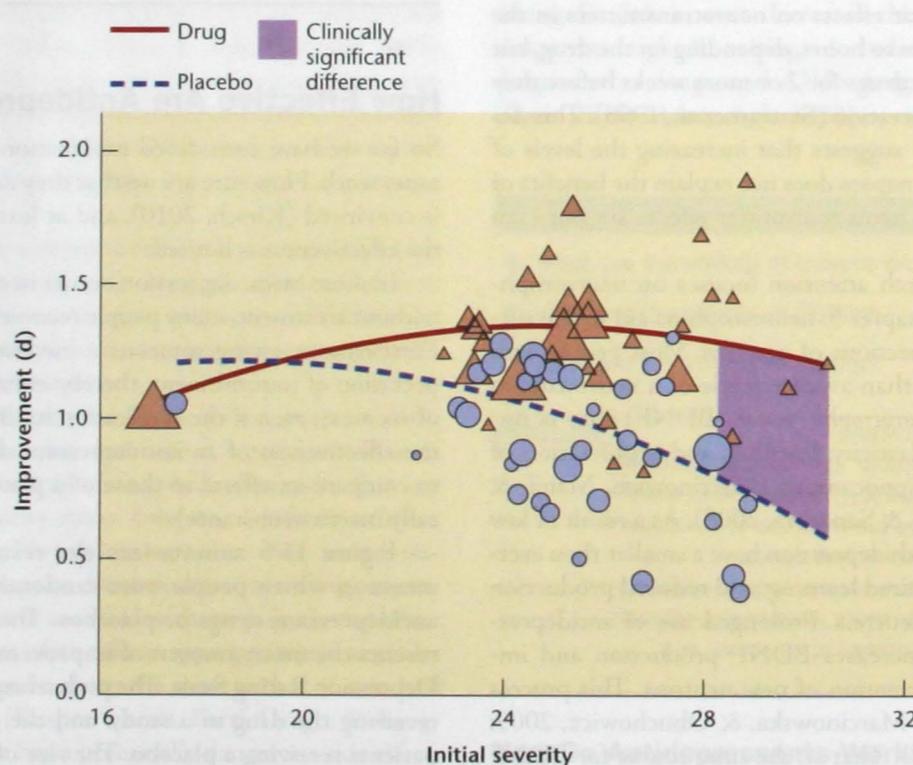


FIGURE 15.6 Mean improvement from depression by people taking antidepressants or placebos

Pink triangles represent people taking medications in a particular study. Gray circles represent people taking placebos. The size of the triangle or circle is proportional to the number of people in the study. (From Kirsch, 2008)

STOP & CHECK

10. As depression becomes more severe, what happens to the percentage of patients showing improvement while taking antidepressant drugs or placebos?

11. What is an advantage of psychotherapy over antidepressant drugs?

ANSWERS

- multiple disorders or people who suffered abuse or neglect in childhood.
10. For more severe cases, the percentage of patients who improve remains about the same for patients taking antidepressant drugs, but fewer patients taking placebo show improvement.
11. People who respond to psychotherapy have a lower risk of later relapse than people who respond to antidepressant drugs.

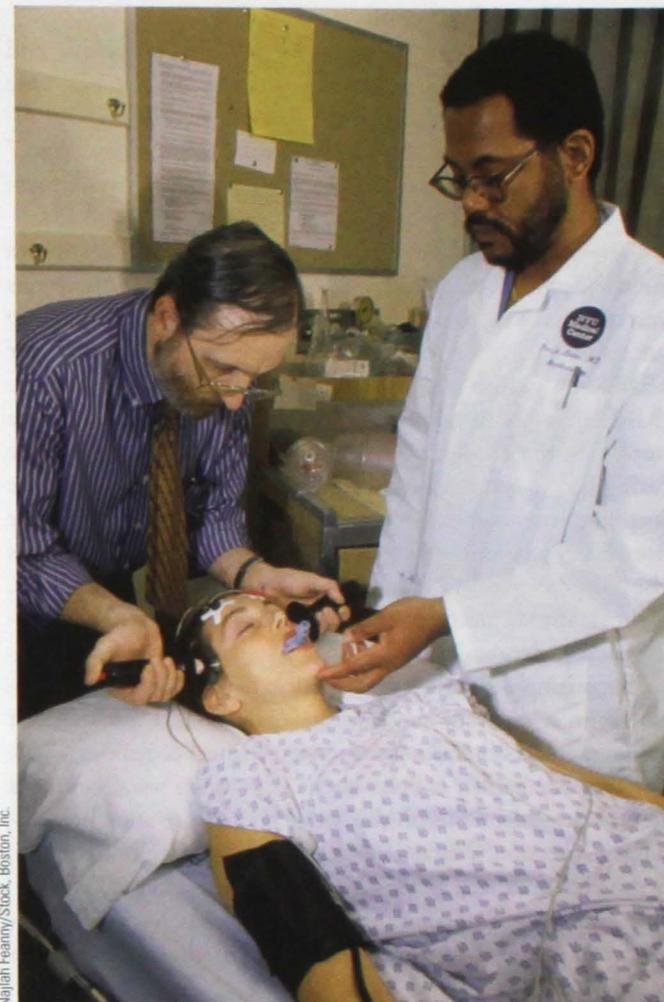


FIGURE 15.7 Electroconvulsive therapy (ECT)

In contrast to an earlier era, ECT today is administered with muscle relaxants or anesthetics to minimize discomfort and only if the patient gives informed consent.

Electroconvulsive Therapy (ECT)

Many people with depression do not respond well to either drugs or psychotherapy. What options are available for them? One possibility, despite its stormy history, is treatment through an electrically induced seizure, known as **electroconvulsive therapy (ECT)**. ECT originated with the observation that for people with both epilepsy and schizophrenia, as symptoms of one disorder increase, symptoms of the other often decrease (Trimble & Thompson, 1986). In the 1930s, Ladislas Meduna tried to relieve schizophrenia by inducing convulsions. Soon, other physicians were doing the same, inducing seizures with a large dose of insulin. Insulin shock is a dreadful experience, however, and difficult to control. An Italian physician, Ugo Cerletti, after years of experimentation with animals, developed a method of inducing seizures with an electric shock through the head (Cerletti & Bini, 1938). Electroconvulsive therapy is quick, and most patients awaken calmly without remembering it.

When ECT proved to be not very effective with schizophrenia, you might guess that psychiatrists would abandon it. Instead, they tried it for other mental hospital patients, despite having no theoretical basis. ECT did indeed relieve depression in many cases. However, its misuse during the 1950s earned it a bad reputation, as some patients were given ECT hundreds of times without their consent.

When antidepressant drugs became available in the late 1950s, the use of ECT declined abruptly. However, it made a partial comeback in the 1970s. ECT today is used only with informed consent, usually for patients with severe depression who have not responded to antidepressant drugs (Reisner, 2003). It is usually applied every other day for about 2 weeks. Patients are given muscle relaxants or anesthetics to minimize discomfort and the possibility of injury (Figure 15.7).

The most common side effect of ECT is memory loss, but limiting the shock to the right hemisphere reduces the memory loss. In any case, the memory impairment lasts no more than a few months, not forever (Reisner, 2003). Besides the threat of

memory loss, the other serious drawback to ECT is the high risk of relapsing into another episode of depression within a few months (Riddle & Scott, 1995). After ECT has relieved depression, the usual strategy is to try to prevent a relapse by means of drugs, psychotherapy, or periodic ECT treatments (Swoboda, Conca, König, Waanders, & Hansen, 2001).

More than half a century after the introduction of ECT, no one is yet sure how it relieves depression, but like antidepressant drugs, ECT increases the proliferation of new neurons in the hippocampus (Perera et al., 2007). It also alters the expression of at least 120 genes in the hippocampus and frontal cortex alone (Altar et al., 2004).

A similar treatment is repetitive transcranial magnetic stimulation. An intense magnetic field is applied to the scalp, stimulating the axons near the surface of the brain. This procedure is moderately effective against depression, although its mechanism of behavioral effect is not known (Ridding & Rothwell, 2007).

Altered Sleep Patterns

Almost everyone with depression has sleep problems, and the sleep problems generally precede the mood changes. One study identified teenagers who reported almost daily problems in falling asleep or staying asleep. Within the next 6 to 7 years, more than half of these young people developed depression (Roane & Taylor, 2008).

The usual sleep pattern for a depressed person resembles the sleep of healthy people who travel a couple of time zones west and have to go to bed later than usual: They fall asleep but awaken early, unable to get back to sleep, and they enter REM sleep within 45 minutes after going to sleep, as Figure 15.8 illustrates. In addition, people who are depressed have more than the average number of eye movements per minute during REM sleep. Many of their relatives show these same sleep patterns, and the relatives who show these patterns are more likely to become depressed themselves than are relatives who sleep normally (Modell, Ising, Holsboer, & Lauer, 2005). In short, altered sleep is a lifelong trait of people who are predisposed to depression.

Surprisingly, although most people feel worse after a sleepless night, a night of total sleep deprivation is the quickest known method of relieving depression (Ringel & Szuba, 2001). However, the benefit is brief, as the depression usually returns after the next night's sleep. Also, while sleep deprivation helps alleviate depression, it increases sensitivity to pain (Kundermann, Hemmeter-Spernal, Huber, Krieg, & Lautenbacher, 2008).

A more practical solution is to alter the sleep schedule, going to bed earlier than usual. The person might still awaken in

the very early morning, but by that time he or she would have received seven or eight hours of sleep. This procedure relieves depression for at least a week in most patients and often longer (Riemann et al., 1999).

Researchers cannot yet explain how sleep deprivation or rescheduling produces mood benefits. A better understanding might lead to other treatments for depression.

STOP & CHECK

12. How can one decrease the memory loss associated with ECT?
13. What change in sleep habits sometimes relieves depression?

ANSWERS

12. Go to bed earlier sometimes relieves depression.
 13. Getting people with depression to go to bed earlier sometimes relieves depression.

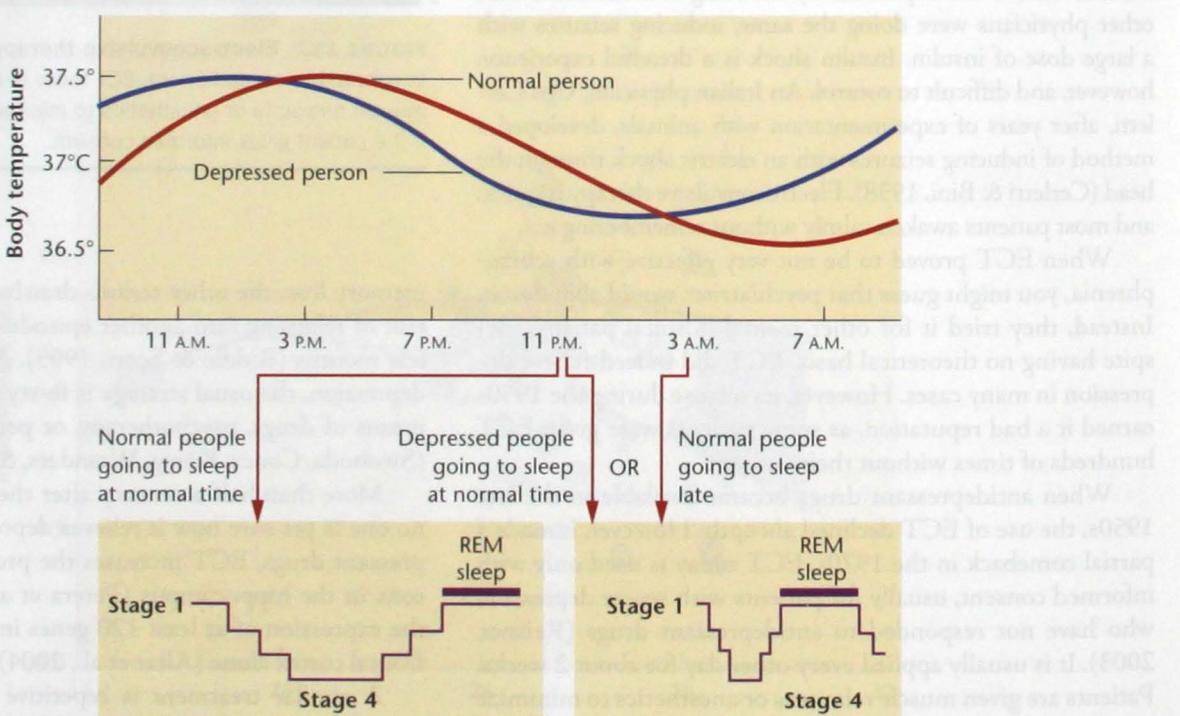


FIGURE 15.8 Circadian rhythms and depression

Most people with depression have their circadian rhythms advanced by several hours. They sleep as if they had gone to bed later than they actually did. (Bottom graphs from *Sleep* by J. Allan Hobson, ©1989, 1995 by J. Allan Hobson. Reprinted by permission of Henry Holt and Company, LLC.)

Many studies have shown that active people are less likely than sedentary people to become depressed. However, most of these studies are correlational in nature and do not support a cause-and-effect conclusion. A few controlled experiments have yielded inconclusive results (Teychenne, Ball, & Salmon, 2010). Still, exercise increases blood flow to the brain and provides other benefits, without the costs or risks of other treatments (Hillman, Erickson, & Kramer, 2008; Hunsberger et al., 2007). More research is necessary, but in the meantime, exercise is a good recommendation.

I Bipolar Disorder

Depression can be either unipolar or bipolar. People with **unipolar disorder** vary between normality and one pole—depression. People with **bipolar disorder**, formerly known as *manic-depressive disorder*, alternate between two poles—depression and its opposite, mania. **Mania** is characterized by restless activity, excitement, laughter, self-confidence, rambling speech, and loss of inhibitions. People with mania become dangerous to themselves and others. Figure 15.9 shows the brain's increase in glucose use during mania and its decrease during depression (Baxter et al., 1985).

People who have full-blown episodes of mania are said to have **bipolar I disorder**. People with **bipolar II disorder** have milder manic phases, called hypomania, characterized by agitation or anxiety. In addition to the mood swings, most people with bipolar disorder have attention deficits, poor impulse control, and impairments of verbal memory (Quraishi & Frangou, 2002). Diagnoses of bipolar disorder have been increasing since the 1990s, especially among teenagers and young adults (Moreno et al., 2007). It is now estimated that about 1% of people will have bipolar I disorder at some time in life, another 1% will have bipolar II disorder, and 2% to 3% will have "subthreshold" bipolar disorder—a minor case not quite strong enough for a diagnosis of bipolar disorder (Merikangas et al., 2007).

Genetics

A genetic predisposition for bipolar disorder is supported by the usual types of evidence—twin studies and adoption studies. In addition, researchers have located two genes that appear to increase the probability of bipolar II disorder (Nwulia et al., 2007). They have also demonstrated that some of the same genes that predispose to major depression also predispose to bipolar disorder (Liu et al., 2011). However, the genes merely increase the risk. None of the genes shows a strong relationship to the disorder.

Treatments

The first successful treatment for bipolar disorder, and still the most common one, is **lithium salts**. Lithium's benefits were discovered accidentally by an Australian investigator, J. F. Cade, who believed uric acid might relieve mania and depression. Cade mixed uric acid (a component of urine) with a lithium salt to help it dissolve and then gave the solution to

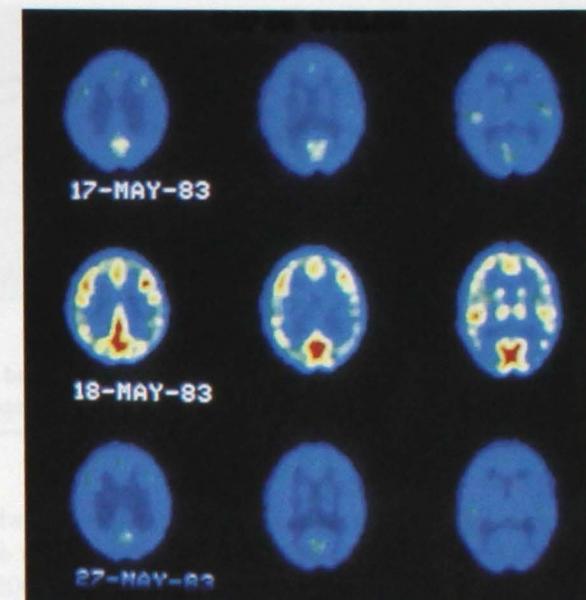


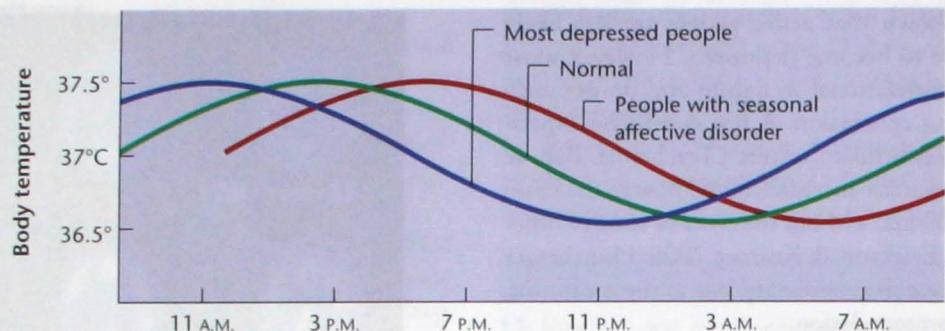
FIGURE 15.9 PET scans for a patient with bipolar disorder

Horizontal planes through three levels of the brain are shown for each day. On May 17 and May 27, when the patient was depressed, brain metabolic rates were low. On May 18, when the patient was in a cheerful, hypomanic mood, the brain metabolic rate was high. Red indicates the highest metabolic rate, followed by yellow, green, and blue. (Reprinted by permission from Macmillan Publishers Ltd: *Nature, A functional neuroanatomy of hallucinations in schizophrenia*, Silbersweig et al., 1995.)

patients. It was indeed helpful, although investigators eventually realized that lithium was the effective agent, not uric acid.

Lithium stabilizes mood, preventing a relapse into either mania or depression. The dose must be regulated carefully, as a low dose is ineffective and a high dose is toxic (Schou, 1997). Two other effective drugs are valproate (trade names Depakene, Depakote, and others) and carbamazepine. If these drugs are not fully effective, physicians sometimes supplement them with antidepressant drugs or antipsychotic drugs—the ones also prescribed for schizophrenia. Antidepressant drugs are risky, as they sometimes provoke a switch from depression to mania. Antipsychotic drugs can be helpful, but they also produce unpleasant side effects.

Lithium, valproate, and carbamazepine have many effects on the brain. A good research strategy is to assume that they relieve bipolar disorder because of some effect they have in common. One effect they share is that they decrease the number of AMPA type glutamate receptors in the hippocampus (Du et al., 2008). Excessive glutamate activity is responsible for some aspects of mania. Also, the drugs that are effective against bipolar disorder block the synthesis of a brain chemical called *arachidonic acid*, which is produced during brain inflammation (S. I. Rapoport & Bosetti, 2002). Bipolar patients show an increased expression of genes associated with inflammation (Padmos et al., 2008). The effects of arachidonic acid are also counteracted by omega-3 fatty acids, such as those in

**FIGURE 15.10** Circadian rhythms for major depression and seasonal affective disorder (SAD)

Patients with SAD are phase-delayed whereas most other patients with depression are phase-advanced. (© Cengage Learning 2013)

seafood, and epidemiological studies suggest that people who eat at least a pound (0.45 kg) of seafood per week have a decreased risk of bipolar disorder (Noaghiul & Hibbeln, 2003).

Another possible treatment relates to sleep. Patients with bipolar disorder during the depressed phase tend to stay in bed for many hours. During the manic phase, they awaken early, reach their activity peak earlier in the day than most people, and get relatively little sleep (Salvatore et al., 2008). Preliminary studies suggest that getting people to maintain a consistent sleeping schedule in a dark, quiet room reduces the intensity of mood swings (Wehr et al., 1998).

STOP & CHECK

14. What are two common treatments for bipolar disorder?

ANSWER

lithium salts and certain anticonvulsant drugs—valproate and carbamazepine.

I Seasonal Affective Disorder

One more form of depression is **seasonal affective disorder (SAD)**—depression that recurs during a particular season, such as winter. SAD is most prevalent near the poles, where the winter nights are long (Haggarty et al., 2002).

MODULE 15.1 ■ IN CLOSING

Biology of Mood Swings

There is nothing abnormal about feeling sad or happy if something unusually bad or good has just happened to you. For people with major depression or bipolar disorder, mood becomes largely independent of events. A traumatic experience might trigger a bout of depression, but once someone has be-

SAD differs from other types of depression in many ways. For example, patients with SAD have phase-delayed sleep and temperature rhythms—becoming sleepy and wakeful later than normal—unlike most other patients with depression, whose rhythms are phase-advanced (Teicher et al., 1997) (Figure 15.10). Also, SAD is seldom as severe as major depression. Many people with SAD have a mutation in one of the genes responsible for regulating the circadian rhythm, as discussed in Chapter 9 (Johansson et al., 2003).

It is possible to treat SAD with very bright lights (e.g., 2,500 lux) for an hour or more each day. The bright light treatment is effective in the morning, afternoon, or evening (Eastman, Young, Fogg, Liu, & Meaden, 1998; Lewy et al., 1998; Terman, Terman, & Ross, 1998). Although its benefits are as yet unexplained, they are substantial. Bright light is less expensive than the other antidepressant therapies and produces its benefits more rapidly, often within 1 week (Kripke, 1998).

STOP & CHECK

15. What are the advantages of bright light treatment compared to antidepressant drugs?

ANSWER

It is cheaper, has no side effects, and produces its benefits more quickly.

SUMMARY

1. People with major depression find that almost nothing makes them happy. In most cases, depression occurs as a series of episodes. 446
2. Depression has a genetic predisposition, but no one gene has a strong effect by itself. 447
3. Uncommonly, depression can be a reaction to a virus, or possibly to hormonal changes. 448
4. Depression is associated with decreased activity in the left hemisphere of the cortex. 449
5. Several kinds of antidepressant drugs are in wide use. Tricyclics block reuptake of serotonin and catecholamines. SSRIs block reuptake of serotonin. SNRIs block reuptake of both serotonin and norepinephrine. MAOIs block an enzyme that breaks down catecholamines and serotonin. Atypical antidepressants are a miscellaneous group with diverse effects. 449
6. Antidepressants alter synaptic activity quickly, but their effects on behavior require at least 2 weeks. Although different drugs affect different neurotransmitters, they all appear to be about equally effective. It is possible that their well-known effects on neurotransmitters are not the main reason for their effects on behavior. 450
7. Most people with depression have a deficiency of the neurotrophin BDNF, which promotes development of new neurons, synapses, and learning in the hippocampus. Most antidepressant drugs produce a gradual increase in BDNF, and therefore enhance synaptic plasticity in the hippocampus. The effects on BDNF may be the main reason for the drugs' benefits. 451
8. Antidepressant drugs are ineffective for many people. For depressed patients with mild to moderate depression, antidepressants are not significantly more effective than placebos. 451
9. Psychotherapy is about as effective as antidepressant drugs for patients with all levels of severity. Psychotherapy is more likely than antipsychotic drugs to produce long-lasting benefits that prevent or delay a relapse after the end of treatment. 452
10. Other therapies for depression include electroconvulsive therapy, altered sleep patterns, and exercise. 453
11. People with bipolar disorder alternate between depression and mania. Effective therapies include lithium salts and certain other drugs. A consistent sleep schedule is also recommended. 455
12. Seasonal affective disorder is marked by recurrent depression during one season of the year. Exposure to bright lights is usually effective in treating it. 456

KEY TERMS

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary, which begins on page 567. Interactive flashcards and crossword puzzles are among the online resources available to help you learn these terms and the concepts they represent.

atypical antidepressants	450	major depression	446
bipolar disorder	455	mania	455
bipolar I disorder	455	monoamine oxidase inhibitors (MAOIs)	450
bipolar II disorder	455	postpartum depression	448
electroconvulsive therapy (ECT)	453	seasonal affective disorder (SAD)	456
lithium	455	selective serotonin reuptake inhibitors (SSRIs)	450
		serotonin norepinephrine reuptake inhibitors (SNRIs)	450
		tricyclics	449
		unipolar depression	455

THOUGHT QUESTIONS

1. Some people have suggested that ECT relieves depression by causing people to forget the events that caused it. What evidence opposes this hypothesis?
2. Certain people suffer from what they describe as "post-Christmas depression," a feeling of letdown after all the excitement of the holiday season. What other explanation can you offer?



MODULE 15.2

Schizophrenia

Here is a conversation between two people diagnosed with schizophrenia (Haley, 1959, p. 321):

- A: Do you work at the air base?
 B: You know what I think of work. I'm 33 in June, do you mind?
 A: June?
 B: 33 years old in June. This stuff goes out the window after I live this, uh—leave this hospital. So I can't get my vocal cords back. So I lay off cigarettes. I'm in a spatial condition, from outer space myself....
 A: I'm a real spaceship from across.
 B: A lot of people talk that way, like crazy, but "Believe It or Not," by Ripley, take it or leave it—alone—it's in the *Examiner*, it's in the comic section, "Believe It or Not," by Ripley, Robert E. Ripley, believe it or not, but we don't have to believe anything, unless I feel like it. Every little rosette—too much alone.
 A: Yeah, it could be possible.
 B: I'm a civilian seaman.
 A: Could be possible. I take my bath in the ocean.
 B: Bathing stinks. You know why? 'Cause you can't quit when you feel like it. You're in the service.

People with schizophrenia say and do things that other people (including other people with schizophrenia) find difficult to understand. The causes of the disorder are not well understood, but they include a large biological component.

I Diagnosis

Schizophrenia was originally called *dementia praecox*, which is Latin for "premature mental deterioration." In 1911, Eugen Bleuler introduced the term *schizophrenia*. Although the term is Greek for "split mind," it is not related to *dissociative identity disorder* (previously known as *multiple personality disorder*), in which someone alternates among different personalities. What Bleuler meant by *schizophrenia* was a split between the

emotional and intellectual aspects of experience: The person's emotional expression or lack of it seems unconnected with current experiences. For example, someone might giggle or cry for no apparent reason or show no reaction to bad news. Not all patients show this detachment of emotion from intellect, but the term lives on.

Diagnosis of schizophrenia is difficult. In most areas of medicine, a physician can confirm a diagnosis with a lab test of some sort. Psychiatry has no dependable lab tests. Psychiatrists rely on behavioral observations, and many cases leave room for uncertainty.

According to the DSM-IV (American Psychiatric Association, 1994), to be diagnosed with **schizophrenia**, someone must have deteriorated in everyday functioning (work, interpersonal relations, self care, etc.) for at least 6 months, and must show at least two of the following, that are not attributable to other disorders:

- **Delusions** (unjustifiable beliefs, such as "Beings from outer space are controlling my actions")
- **Hallucinations** (false sensory experiences, such as hearing voices when alone)
- Disorganized speech (rambling or incoherent)
- Grossly disorganized behavior
- Weak or absent signs of emotion, speech, and socialization

Each of these is a judgment call. Sometimes a statement that appears to be a delusion ("People are persecuting me") is actually true, or at least defensible. Many healthy people have heard a voice when they knew they were alone, at least once or twice. The term "grossly disorganized behavior" encompasses a wide variety of possibilities. The symptoms vary so greatly that you could easily find several people diagnosed with schizophrenia who have almost nothing in common (Andreasen, 1999).

The first four items on the list—delusions, hallucinations, disorganized speech, and disorganized behavior—are called **positive symptoms** (behaviors that are present that should be absent). Weak or absent emotion, speech, and socialization are **negative symptoms** (behaviors that are absent that should



Nancy C. Andreasen

Being a scientist and a clinician is a double privilege. We actually get paid to spend our time asking both scientific and clinical questions that everyone would like to ask and have answered, and people grant us the trust of sharing their most intimate thoughts and experiences with us.

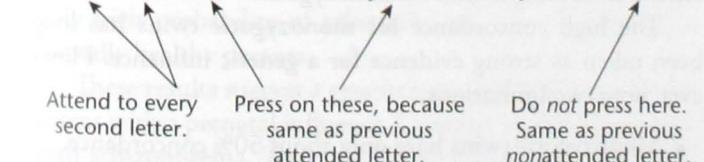
be present). Negative symptoms are usually stable over time and difficult to treat.

It is also useful to distinguish *cognitive* symptoms. The cognitive symptoms are limitations of thought and reasoning that are common in schizophrenia, even if they are not central to the diagnosis. Overall intelligence varies considerably, but on average, IQ scores are a few points below those of the rest of the population (Woodberry, Giuliano, & Seidman, 2008). The most typical type of thought disorder of schizophrenia is a difficulty understanding and using abstract concepts. Related symptoms include deficits in attention and working memory (Hanlon et al., 2005).

Which of the various symptoms, if any, is the primary problem? According to Nancy Andreasen (1999), a leading investigator of schizophrenia, the main problem is disordered thoughts that result from abnormal interactions between the cortex and the thalamus and cerebellum. The disordered thinking may lead to the hallucinations, delusions, and other symptoms.

One way to test this idea is to see whether we could make normal, healthy people talk or behave in incoherent ways if we overtaxed their working memory. Imagine yourself in the following study. The researcher shows a series of pictures for 30 seconds each, and you are supposed to tell a short story about each one. If you see the same picture a second time, you should tell a totally new story about it, unlike your first one. Furthermore, on some trials, you have an additional task to burden your memory while you are trying to tell a story: A series of letters appears on the screen, one at a time. You should pay attention to every second letter. Whenever it is the same as the last letter that you paid attention to, you should press a key. For example,

D L K F R F B L M T J T X H Q U B R N



Most people's speech becomes less clear when they perform this memory task while trying to tell a story. If it is the second presentation of a picture, requiring them to avoid what they said the first time and tell a totally new story, the memory task causes even greater interference, and their speech becomes incoherent, somewhat like schizophrenic speech (Kerns, 2007). The implication is that memory impairment could be the central symptom.

STOP & CHECK

16. Why are hallucinations considered a positive symptom?

- ANSWER**
 16. Hallucinations are considered a positive symptom because they are present when they should be absent. A "positive" symptom is not a "good" symptom.

APPLICATIONS AND EXTENSIONS

Differential Diagnosis of Schizophrenia

In the rules for diagnosing schizophrenia, did you notice the expression "not attributable to other disorders"? Even if someone's symptoms match the description of schizophrenia perfectly, it is important to make a **differential diagnosis**—that is, one that rules out other conditions with similar symptoms. Here are a few conditions that sometimes resemble schizophrenia:

- **Mood disorder with psychotic features:** People with depression frequently have delusions, especially delusions of guilt or failure. Some report hallucinations also.
- **Substance abuse:** Many of the positive symptoms of schizophrenia can develop from prolonged use of amphetamine, methamphetamine, cocaine, LSD, or phencyclidine ("angel dust"). Someone who stops taking the drugs is likely, though not certain, to recover from these symptoms. Substance abuse is more likely than schizophrenia to produce visual hallucinations.
- **Brain damage:** Damage or tumors in the temporal or prefrontal cortex often produce some of the symptoms of schizophrenia.
- **Undetected hearing deficits:** Sometimes, someone who is starting to have trouble hearing thinks that everyone else is whispering and starts to worry, "They're whispering about me!" Delusions of persecution can develop.
- **Huntington's disease:** The symptoms of Huntington's disease include hallucinations, delusions, and disordered thinking, as well as motor symptoms. An uncommon type of schizophrenia, catatonic schizophrenia, includes motor abnormalities, so a mixture of psychological and motor symptoms could represent either schizophrenia or Huntington's disease.
- **Nutritional abnormalities:** Niacin deficiency can produce hallucinations and delusions (Hoffer, 1973), and so can a deficiency of vitamin C or an allergy to milk proteins (not the same as lactose intolerance). Some people who cannot tolerate wheat gluten or other proteins react with hallucinations and delusions (Reichelt, Seim, & Reichelt, 1996). ■

Demographic Data

Worldwide, about 1% of people suffer from schizophrenia at some point in life (Narrow et al., 2002; Perälä et al., 2007). The estimate rises or falls depending on how many mild cases we include. Since the mid-1900s, the reported prevalence of schizophrenia has been declining in many countries (Suisvaaari, Haukka, Tanskanen, & Lönnqvist, 1999; Torrey & Miller, 2001). Is schizophrenia actually less common, or are psychiatrists just diagnosing it differently? This is not an easy question to answer. However, even when it is diagnosed today, it appears to be less severe than it often used to be. Perhaps our society is doing something to prevent schizophrenia without knowing what.

Schizophrenia occurs in all ethnic groups and all parts of the world. However, it is significantly more common in cities than in rural areas, for reasons unknown (Kelly et al., 2010). Also it is 10 to 100 times more common in the United States and Europe than in most Third World countries (Torrey, 1986). Part of that discrepancy could be due to differences in recordkeeping, but other possibilities exist, including social support and diet. A diet high in sugar and saturated fat, as is common in prosperous countries, aggravates schizophrenia, whereas a diet rich in fish alleviates it (Peet, 2004). Omega-3 fatty acids, abundant in seafood, increase production of BDNF, increase production of new cells in the hippocampus, and block apoptosis and other neural damage (V. R. King et al., 2006; Venna, 2008).

Lifetime prevalence of schizophrenia is more common for men than women by a ratio of about 7:5. On average, it is also more severe in men and has an earlier onset—usually in the teens or early 20s for men and the mid to late 20s for women (Aleman, Kahn, & Selten, 2003).

Researchers have documented several unexplained oddities about schizophrenia. The points that follow do not fit neatly into any currently prominent theory. They indicate how many mysteries remain:

- Schizophrenia is significantly less common than average among people with type 1 (juvenile-onset) diabetes, although it is more common than average in people with type 2 (adult-onset) diabetes (Juvonen et al., 2007).
 - People with schizophrenia have an increased risk of colon cancer but below average probability of respiratory cancer or brain cancer (Hippisley-Cox, Vinogradova, Coupland, & Parker, 2007; Roppel, 1978).
 - People with schizophrenia seldom develop rheumatoid arthritis or allergies (Goldman, 1999; Rubinstein, 1997).
 - Women who have a schizophrenic breakdown during pregnancy usually give birth to daughters. However, those who have a breakdown shortly after giving birth usually give birth to sons (M. A. Taylor, 1969).
 - Many people with schizophrenia have a characteristic body odor, attributed to the chemical *trans*-3-methyl-2-hexenoic acid, and decreased ability to smell that
- chemical themselves (Brewer et al., 2007; K. Smith, Thompson, & Koster, 1969).
- Most people with schizophrenia and many of their unaffected relatives have deficits in pursuit eye movements—the ability to keep their eyes on a moving target (Keefe et al., 1997; Sereno & Holzman, 1993).

STOP & CHECK

17. Has the reported prevalence of schizophrenia been increasing, decreasing, or staying the same?

ANSWER

17. Schizophrenia has been decreasing in reported prevalence.

Genetics

Huntington's disease (Chapter 8) can be called a genetic disease: By examining part of chromosome 4, one can predict with almost perfect accuracy who will develop the disease and who will not. At one time, many researchers believed that schizophrenia might be a genetic disease in the same sense. However, accumulating evidence indicates that although schizophrenia has a genetic basis, it does not depend on any single gene.

Twin Studies

The more closely you are biologically related to someone with schizophrenia, the greater your own probability of schizophrenia, as shown in Figure 15.11 (Gottesman, 1991). One of the most important points in Figure 15.11, confirmed by other studies (Cardno et al., 1999), is that monozygotic twins have a much higher **concordance** (agreement) for schizophrenia than do dizygotic twins. Furthermore, twin pairs who are really monozygotic, but thought they weren't, are more concordant than twin pairs who thought they were, but really aren't (Kendler, 1983). That is, *being* monozygotic is more critical than *treated as* monozygotic.

The high concordance for monozygotic twins has long been taken as strong evidence for a genetic influence. However, note two limitations:

- Monozygotic twins have only about 50% concordance, not 100%. Monozygotic twins could differ because a gene is activated in one individual and suppressed in another (Tsujita et al., 1998), or they could differ because of environmental influences.
- In Figure 15.11, note the greater similarity between dizygotic twins than between siblings. Dizygotic twins have the same genetic resemblance as siblings but greater environmental similarity, including prenatal environment.

Percent developing schizophrenia

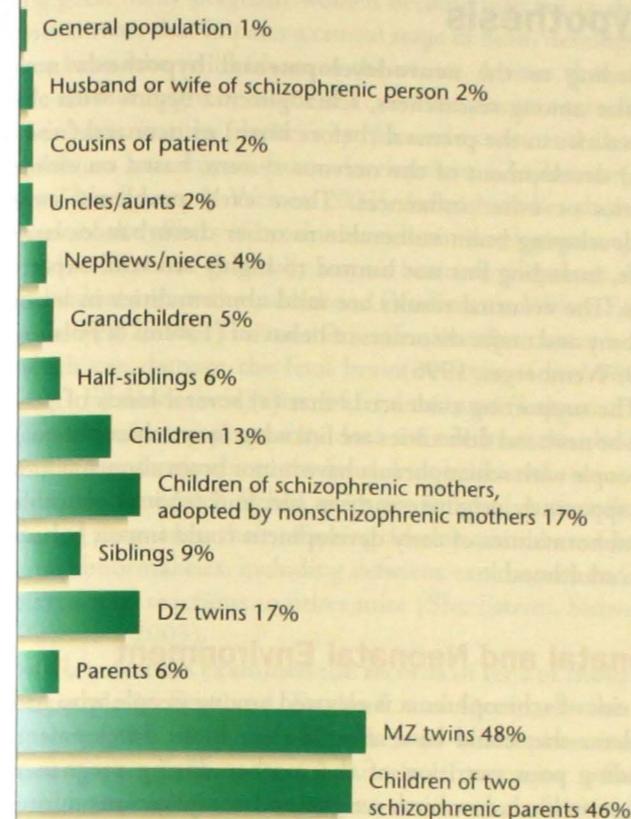


FIGURE 15.11 Probabilities of developing schizophrenia

People with a closer genetic relationship to someone with schizophrenia have a higher probability of developing it themselves. (Based on data from Gottesman, 1991)

Adopted Children Who Develop Schizophrenia

When an adopted child develops schizophrenia, the disorder is more common in the person's biological relatives than adopting relatives. One Danish study found schizophrenia in 12.5% of the immediate biological relatives and none of the adopting relatives (Kety et al., 1994). Note in Figure 15.11 that children of a mother with schizophrenia have a moderately high probability of schizophrenia, even if adopted by mentally healthy parents.

These results suggest a genetic basis, but they are also consistent with a prenatal influence. Consider a pregnant woman with schizophrenia. True, she passes her genes to her child, but she also provides the prenatal environment. Many women with schizophrenia smoke, drink, use other drugs, and eat a less than desirable diet during pregnancy. A disproportionate number have complications during pregnancy and delivery (Jablensky, Morgan, Zubrick, Bower, & Yellachich, 2005). If some of their children develop schizophrenia, we cannot be sure that the influence is genetic.

Studies on adopted children also support a role for environmental influences. A study of adopted children in Fin-

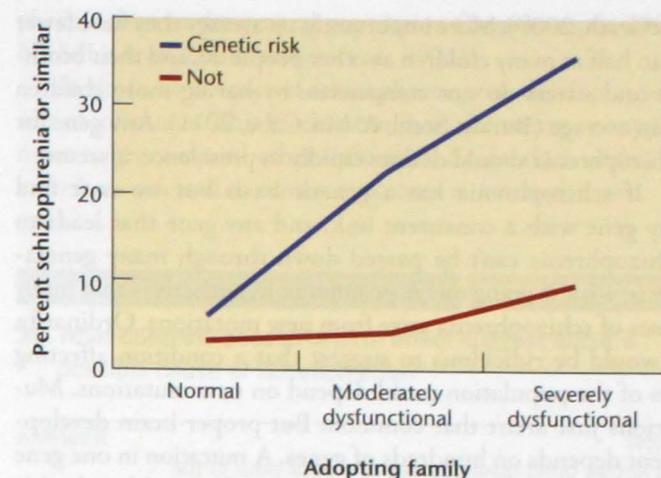


FIGURE 15.12 Probability of schizophrenia or similar conditions in adopted children

The probability was higher for children of a mother with schizophrenia, but growing up in a dysfunctional family magnified that risk. (Based on data from Wynne et al., 2006)

land found a high probability of schizophrenia or related conditions among children who had a biological mother with schizophrenia *and* a severely disordered adopting family. The genetic risk itself or the disordered family itself had less effect, as shown in Figure 15.12 (Wynne et al., 2006).

Efforts to Locate a Gene

The strongest evidence for a genetic influence would be to locate a gene that is consistently linked with schizophrenia. Researchers working with various populations have identified more than a dozen genes that appear to be more common in people with schizophrenia. One that has attracted much interest, called *DISC1* (*disrupted in schizophrenia 1*), controls production of dendritic spines (Hayashi-Takagi et al., 2010) and the generation of new neurons in the hippocampus (Duan et al., 2007). Other genes linked to schizophrenia in several studies are important for brain development (Hall et al., 2006; Stefansson et al., 2009), control of transmission at glutamate synapses (Dickman & Davis, 2009), and connections between the hippocampus and the prefrontal cortex (Esslinger et al., 2009). However, researchers have not had great success at replicating the results from one population to another. A study of nearly 2,000 patients with schizophrenia and a control group found no statistically significant relationship between schizophrenia and any of the 14 genes that previous studies identified as linked to schizophrenia (Sanders et al., 2008).

In a way, these results should not be surprising. If schizophrenia depended on a single gene, it would be hard for that gene to remain in 1% of the population, given the natural selection pressures against it. People with schizophrenia die younger than other people, on average (Saha, Chant, &

McGrath, 2007). More importantly, on average they have fewer than half as many children as other people do, and their brothers and sisters do not compensate by having more children than average (Bundy, Stahl, & MacCabe, 2011). Any gene for schizophrenia should decline rapidly in prevalence, it seems.

If schizophrenia has a genetic basis but we can't find any gene with a consistent link, and any gene that leads to schizophrenia can't be passed down through many generations, what is going on? A prominent hypothesis is that many cases of schizophrenia arise from new mutations. Ordinarily, it would be ridiculous to suggest that a condition affecting 1% of the population could depend on new mutations. Mutations just aren't that common. But proper brain development depends on hundreds of genes. A mutation in one gene is a rare event, but a mutation in any of several hundred is not so rare. An even more likely possibility is deletion of a gene, a fairly common error in reproduction (International Schizophrenia Consortium, 2009). Researchers examined the chromosomes of people with and without schizophrenia and found genetic *microdeletions* and *microduplications* (i.e., elimination or duplication of parts of a gene) in 5% of the control group, 15% of people with schizophrenia, and 20% of people with onset of schizophrenia before age 18 (Walsh et al., 2008). Those microdeletions and microduplications were distributed over a great many genes. Thus, the hypothesis is that a new mutation or deletion of any of a large number of genes disrupts brain development and increases the probability of schizophrenia. As fast as natural selection weeds out those mutations or deletions, new ones arise to replace them.

One observation supporting this idea is that schizophrenia is somewhat more common among children of older fathers (Byrne, Agerbo, Ewald, Eaton, & Mortensen, 2003; Malspina et al., 2002). Women are born with all the eggs they will ever have, but men continue making new sperm throughout life, and the possibility of mutations accumulates over time.

We need not assume that all cases of schizophrenia have a genetic predisposition. Others may depend on prenatal environment or other influences on brain development.

STOP & CHECK

18. The fact that adopted children who develop schizophrenia usually have biological relatives with schizophrenia implies a probable genetic basis. What other interpretation is possible?

19. Does the hypothesis of new mutations conflict with the results showing that an aberrant form of the gene *DISC1* is often linked to schizophrenia?

ANSWERS
18. A biological mother can influence her child's development through prenatal environment as well as genetics, even if the child is adopted early. **19.** No. Although mutations in many genes can, according to the hypothesis, lead to schizophrenia, the *DISC1* gene could be one where the mutation is more certain to cause schizophrenia.

The Neurodevelopmental Hypothesis

According to the **neurodevelopmental hypothesis** now popular among researchers, schizophrenia begins with abnormalities in the prenatal (before birth) or neonatal (newborn) development of the nervous system, based on either genetics or other influences. These early problems leave the developing brain vulnerable to other disturbances later in life, including but not limited to highly stressful experiences. The eventual results are mild abnormalities in brain anatomy and major disorders of behavior (Fatemi & Folsom, 2009; Weinberger, 1996).

The supporting evidence is that (a) several kinds of prenatal or neonatal difficulties are linked to later schizophrenia; (b) people with schizophrenia have minor brain abnormalities that apparently originate early in life; and (c) it is plausible that abnormalities of early development could impair behavior in adulthood.

Prenatal and Neonatal Environment

The risk of schizophrenia is elevated among people who had problems that could have affected their brain development, including poor nutrition of the mother during pregnancy, premature birth, low birth weight, and complications during delivery (Ballon, Dean, & Cadenhead, 2007). The risk is also elevated if the mother was exposed to extreme stress, such as the sudden death of a close relative, early in her pregnancy (Khashan et al., 2008). None of these influences by itself accounts for many cases of schizophrenia, although together their influence is greater (Cannon, Jones, & Murray, 2002).

Schizophrenia has also been linked to head injuries in early childhood (AbdelMalik, Husted, Chow, & Bassett, 2003), although we do not know whether the head injuries led to schizophrenia or early symptoms of schizophrenia increased the risk of head injuries.

If a mother is Rh-negative and her baby is Rh-positive, the baby's Rh-positive blood factor may trigger an immunological rejection by the mother. The response is weak with the woman's first Rh-positive baby but stronger in later pregnancies, and it is more intense with boy than girl babies. Second- and later-born boy babies with Rh incompatibility have an increased risk of hearing deficits, mental retardation, and several other problems, and about twice the usual probability of schizophrenia (Hollister, Laing, & Mednick, 1996).

Another suggestion of prenatal influences comes from the **season-of-birth effect**: the tendency for people born in winter to have a slightly (5% to 8%) greater probability of developing schizophrenia than people born at other times of the year. This tendency is particularly pronounced in latitudes far from the equator (Davies, Welham, Chant, Torrey, & McGrath, 2003; Torrey, Miller, et al., 1997).

What might account for this effect? One possibility is complications of delivery or early nutrition (Jablensky et al., 2005). Another is viral infection. Influenza and other viral

epidemics are most common in the fall. Therefore, the reasoning goes, many pregnant women become infected in the fall with a virus that impairs a crucial stage of brain development in a baby who will be born in the winter. A virus that affects the mother might or might not cross the placenta into the fetus's brain, but the mother's cytokines do cross, and excessive cytokines can impair brain development (Zuckerman, Rehavi, Nachman, & Weiner, 2003). Animal studies show that some of the effects of cytokines on brain development appear mild at first but gradually impair brain development as the individual approaches adulthood (Vuillermot, Weber, Feldon, & Meyer, 2010). The mother's infection also causes a fever, which can damage the fetal brain. A fever of just 38.5°C (101°F) slows the division of fetal neurons (Laburn, 1996). (Exercise during pregnancy does *not* overheat the abdomen and is not dangerous to the fetus. Hot baths and saunas may be risky, however.) When mice are infected with influenza during pregnancy, their offspring develop a number of behavioral abnormalities, including deficient exploration and deficient social reactions to other mice (Shi, Fatemi, Sidwell, & Patterson, 2003).

Researchers examined the records of tens of thousands of people in Scotland, England, and Denmark over several decades. They found increased schizophrenia rates among people born 2 to 3 months after major influenza epidemics, such as the one in the autumn of 1957 (Adams, Kendell, Hare, & Munk-Jørgensen, 1993). Other studies retrieved blood samples that hospitals had taken from pregnant women and stored for decades. Researchers found increased incidence of influenza virus among mothers whose children eventually developed schizophrenia (A. S. Brown et al., 2004; Buka et al., 2001). Rates of schizophrenia are also increased among offspring of mothers who had rubella (German measles), herpes, and other infections during pregnancy (A. S. Brown et al., 2001; Buka et al., 2008).

Certain childhood infections may also relate to schizophrenia. The parasite *Toxoplasma gondii* (discussed also in Chapter 12 in the context of anxiety and the amygdala) reproduces only in cats, but it can infect humans and other species also. If it infects the brain of an infant or child, it impairs brain development and leads to memory disorder, hallucinations, and delusions (Torrey & Yolken, 2005). People who develop schizophrenia in adulthood are more likely than other people to have had a pet cat in childhood (Torrey, Rawlings, & Yolken, 2000). Blood tests have found antibodies to the *Toxoplasma* parasite in a higher percentage of people with schizo-

phrenia than in the general population (Leweke et al., 2004; Niebuhr et al., 2008; Yolken et al., 2001).

In short, some cases of schizophrenia may develop as a result of infections. This mechanism is an alternative or supplement to genetics and other influences. Evidently, a variety of influences can lead to similar outcomes in schizophrenia.

STOP & CHECK

20. What does the season-of-birth effect suggest about a possible cause of schizophrenia?

ANSWER

20. The season-of-birth effect is the observation that schizophrenia is slightly more common among people who were born in the winter. One interpretation is that influenza or other infections of the mother during the winter, or other infections of the baby born in the winter, fall impair brain development of a baby born in the winter.

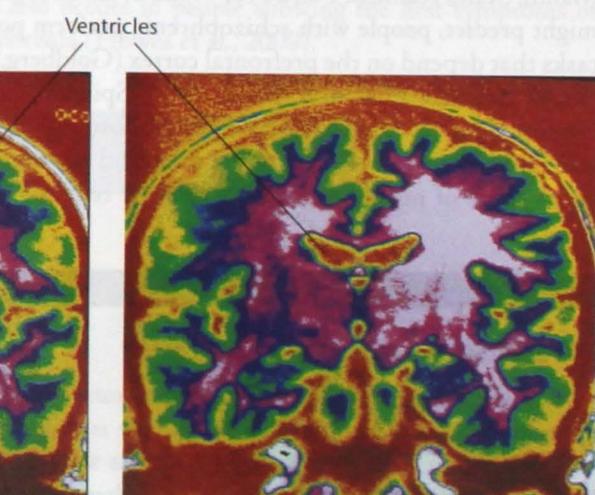


FIGURE 15.13 Coronal sections for identical twins

The twin on the left has schizophrenia; the twin on the right does not. The ventricles (near the center of each brain) are larger in the twin with schizophrenia.

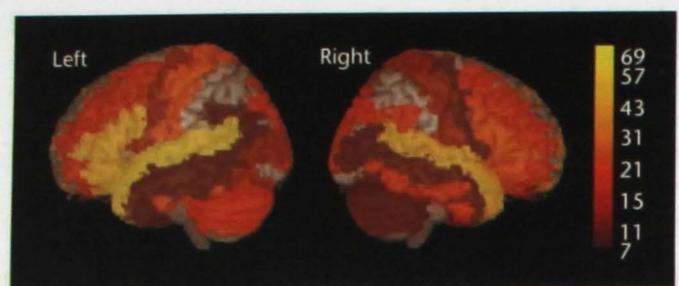


FIGURE 15.14 Cortical areas showing decreased volume in patients with schizophrenia

Areas in yellow showed decreased volume in the largest percentage of studies. Those in various shades of red showed decreases in fewer studies. (From "Regional deficits in brain volume in schizophrenia: A meta-analysis of voxel-based morphometry studies," by R. Honea, T. J., Crow, D., Passingham, and C. E. Mackay, American Journal of Psychiatry, 162, 2233-2245. Reprinted by permission from the American Journal of Psychiatry, Copyright (2005) American Psychiatric Association.)

Passingham, & Mackay, 2005). Note that the strongest deficits were in the left temporal and frontal areas of the cortex. Note also that most cortical areas showed mild abnormalities in at least one or two studies. The thalamus, which is in the interior of the brain and therefore not shown in Figure 15.14, is also smaller than average for people with schizophrenia (Harms et al., 2007).

The areas with consistent signs of abnormality include some that mature slowly, such as the dorsolateral prefrontal cortex (Berman, Torrey, Daniel, & Weinberger, 1992; Fletcher et al., 1998; Gur, Cowell, et al., 2000). The abnormalities include weaker than average connections from the dorsolateral prefrontal cortex to other brain areas, and less than normal activity in this area during tasks requiring attention and memory (Lynall et al., 2010; van den Heuvel, Mandl, Stam, Kahn, & Pol, 2010; Weiss et al., 2009). As you might predict, people with schizophrenia perform poorly at tasks that depend on the prefrontal cortex (Goldberg, Weinberger, Berman, Pliskin, & Podd, 1987; Spindler, Sullivan, Menon, Lim, & Pfefferbaum, 1997). Most patients with schizophrenia show deficits of memory and attention similar to those of people with damage to the temporal or pre-

frontal cortex (Park, Holzman, & Goldman-Rakic, 1995) (Methods 15.1).

At a microscopic level, the most reliable finding is that cell bodies are smaller than normal, especially in the hippocampus and prefrontal cortex (Pierri, Volk, Auh, Sampson, & Lewis, 2001; Rajkowska, Selem, & Goldman-Rakic, 1998; Selem, Rajkowska, & Goldman-Rakic, 1995; Weinberger, 1999).

Lateralization also differs from the normal pattern. In most people, the left hemisphere is slightly larger than the right, especially in the planum temporale of the temporal lobe, but in people with schizophrenia, the right planum temporale is equal or larger (Kasai et al., 2003; Kwon et al., 1999). People with schizophrenia have lower than normal overall activity in the left hemisphere (Gur & Chin, 1999) and are more likely than other people to be left-handed (Satz & Green, 1999). All these results suggest a subtle change in brain development.

The reasons behind the brain abnormalities are not certain. Most researchers have been careful to limit their studies to patients with schizophrenia who have never taken, or who have not recently taken, antipsychotic drugs, so the deficits are not a result of treatments for schizophrenia. However, many people with schizophrenia use alcohol, marijuana, and other drugs, and it is likely that some of the brain abnormalities result from heavy drug use (Rais et al., 2008; Sullivan et al., 2000).

The results are inconsistent as to whether the brain damage associated with schizophrenia is *progressive*—that is, whether it increases over time. The brain damage associated with Parkinson's disease, Huntington's disease, and Alzheimer's disease gets worse as the person ages. Brain abnormalities are found in young people shortly after a diagnosis of schizophrenia (Lieberman et al., 2001), and many studies find that the brain abnormalities are no greater in older patients (Andreasen et al., 1990; Censits, Ragland, Gur, & Gur, 1997; Russell, Munro, Jones, Hemsley, & Murray, 1997; Selem et al., 1995). However, other studies show a moderate degree of increased brain loss as patients age (Cahn et al., 2002; Hulshoff et al., 2001; Mathalon, Sullivan, Lim, & Pfefferbaum, 2001; Rais et al., 2008). Nevertheless, the brains of people with schizophrenia do not show the signs that accompany neuron death—proliferation of glia cells and activation of the genes responsible for repair after injury (Arnold, 2000; Benes, 1995; K. O. Lim et al., 1998). Possibly, the neurons are shrinking without dying.

METHODS 15.1

The Wisconsin Card Sorting Task

Neuropsychologists use many behavioral tests to measure the functioning of the prefrontal cortex. One is the Wisconsin Card Sorting Task. A person is handed a shuffled deck of cards that differ in number, color, and shape of objects—for example, three red circles, five blue triangles, four green squares. First the person is asked to sort them by one rule, such as separate them by color. Then the rule changes, and

the person is supposed to sort them by a different rule, such as number. Shifting to a new rule requires suppressing the old one and evokes activity in the prefrontal cortex (Konishi et al., 1998). People with damage to the prefrontal cortex can sort by whichever rule is first, but then they have trouble shifting to a new rule. People with schizophrenia have the same difficulty. (So do children.)

In any case, most of the damage is apparent early, and later changes are relatively small.

Early Development and Later Psychopathology

One question may have struck you. How can we reconcile the idea of abnormalities in early development with the fact that the disorder is usually diagnosed after age 20? The time course may not be as puzzling as it seems at first (Weinberger, 1996). Most of the people who develop schizophrenia in adulthood had shown other problems since childhood, including deficits in attention, memory, and impulse control (Keshavan, Diwadkar, Montrose, Rajarethnam, & Sweeney, 2005). Furthermore, the prefrontal cortex, an area that shows consistent signs of deficit in schizophrenia, is one of the slowest brain areas to mature. In one study, researchers damaged this area in infant monkeys and tested the monkeys later. At age 1 year, the monkeys' behavior was nearly normal, but by age 2 years, it had deteriorated markedly (P. S. Goldman, 1971, 1976). That is, the effects of the brain damage grew worse over age. Presumably, the effects of brain damage were minimal at age 1 year because the dorsolateral prefrontal cortex doesn't do much at that age anyway. Later, when it should begin assuming important functions, the damage begins to make a difference (Figure 15.15).

STOP & CHECK

21. If schizophrenia is due to abnormal brain development, why do behavioral symptoms not become apparent until later in life?

ANSWER

- early in life, when the prefrontal cortex is contributing little anyway.
early development might not produce any symptoms
reach maturity; therefore, early disruption of this
area's development might not produce any symptoms
22. Parts of the prefrontal cortex are very slow to

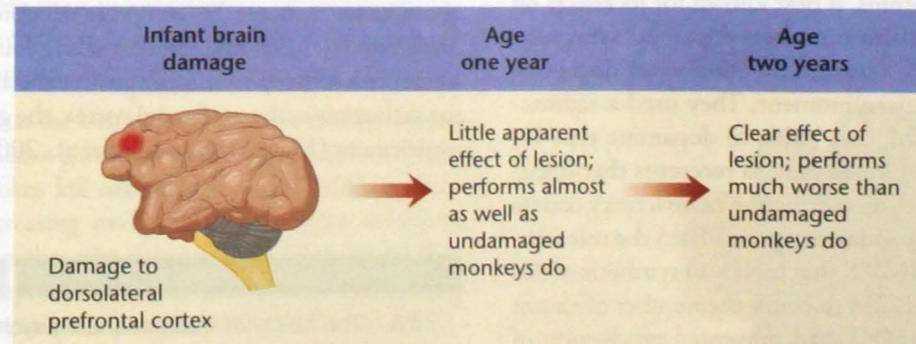


FIGURE 15.15 Delayed effects of brain damage in infant monkeys

After damage to the dorsolateral prefrontal cortex, monkeys are unimpaired at age 1 year but impaired later, when this area ordinarily matures. Researchers speculate that similar damage in humans might produce behavioral deficits not apparent until adulthood. (Based on P. S. Goldman, 1976)

Treatments

Before antipsychotic drugs became available in the mid-1950s, most people with schizophrenia were confined to mental hospitals with little hope of recovery. Today, mental hospitals are far less crowded because of drugs and outpatient treatment.

Antipsychotic Drugs and Dopamine

In the 1950s, psychiatrists discovered that chlorpromazine (trade name Thorazine) relieves the positive symptoms of schizophrenia for most, though not all, patients. Researchers later discovered other **antipsychotic**, or **neuroleptic**, drugs (drugs that tend to relieve schizophrenia and similar conditions) in two chemical families: the **phenothiazines** (FEE-no-THI-uh-zeens), which include chlorpromazine, and the **butyrophenones** (BYOO-tir-oh-FEE-noans), which include haloperidol (trade name Haldol). Behavioral benefits of any of these drugs develop gradually over a month or more. Symptoms generally return after cessation of treatment.

As Figure 15.16 illustrates, each of these drugs blocks dopamine synapses. For each drug, researchers determined the mean dose prescribed for patients with schizophrenia (displayed along the horizontal axis) and the amount needed to block dopamine receptors (displayed along the vertical axis). As the figure shows, the drugs that are most effective against schizophrenia (and therefore used in the smallest doses) are the most effective at blocking dopamine receptors (Seeman, Lee, Chau-Wong, & Wong, 1976).

That finding inspired the **dopamine hypothesis of schizophrenia**, which holds that schizophrenia results from excess activity at dopamine synapses in certain brain areas. Although the concentration of dopamine in the brain is no higher than normal, the turnover is elevated, especially in the basal ganglia (Kumakura et al., 2007). That is, neurons release dopamine at a faster than average rate and synthesize more to replace the molecules that they do not reabsorb. Elevated dopamine release also occurs in people showing the first symptoms of schizophrenia (Howes et al., 2009).

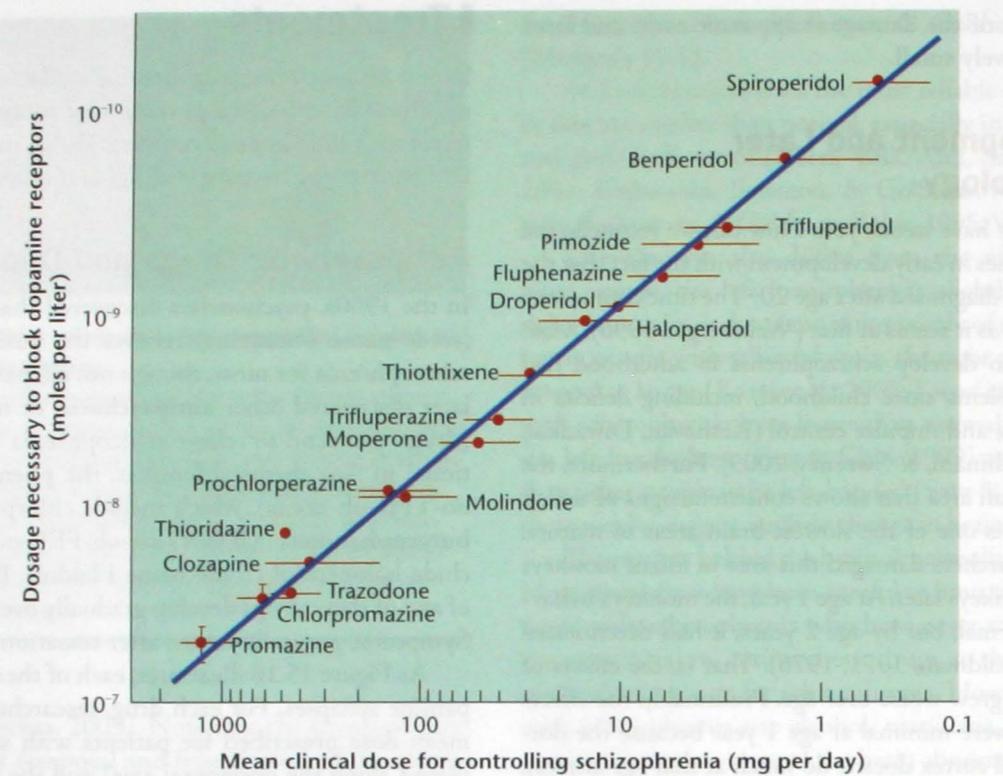


FIGURE 15.16 Dopamine-blocking effects of antipsychotic drugs

Drugs are arranged along the horizontal axis in terms of the average daily dose prescribed for patients with schizophrenia. (Horizontal lines indicate common ranges.) Larger doses are to the left and smaller doses are to the right so that more effective drugs are to the right. Along the vertical axis is a measurement of the amount of each drug required to achieve a certain degree of blockage of postsynaptic dopamine receptors. Larger doses are toward the bottom and smaller doses are toward the top so that the drugs on top are more effective. (From "Antipsychotic Drug Doses and Neuroleptic/Dopamine Receptors," by P. Seeman, T. Lee, M. Chau-Wong, and K. Wong, *Nature*, 261, 1976, pp. 717-719. Copyright © 1976 Macmillan Magazines Limited. Reprinted by permission of *Nature* and Phillip Seeman.)

Further support for the dopamine hypothesis comes from the fact that large, repeated use of amphetamine, methamphetamine, or cocaine induces **substance-induced psychotic disorder**, characterized by hallucinations and delusions, the positive symptoms of schizophrenia. Each of these drugs increases or prolongs the activity at dopamine synapses. LSD, which also produces psychotic symptoms, is best known for its effects on serotonin synapses, but it also stimulates dopamine synapses.

Researchers set out to measure the number of dopamine receptors occupied at a given moment. They used a radioactively labeled drug, IBZM, that binds to dopamine type D₂ receptors. Because IBZM binds only to receptors that dopamine did not already bind, measuring the radioactivity counts the number of vacant dopamine receptors. Then the researchers used a second drug, AMPT, that blocks all synthesis of dopamine and again used IBZM to count the number of vacant D₂ receptors. Because AMPT had prevented production of dopamine, *all* D₂ receptors should be vacant at this time, so the researchers got a count of the total. Then they subtracted the first count from the second count, yielding the number of D₂ receptors occupied by dopamine at the first count:

- First count: IBZM binds to all D₂ receptors not already attached to dopamine.

Role of Glutamate

Abnormalities of dopamine transmission need not be the whole story for schizophrenia. According to the **glutamate hypothesis of schizophrenia**, the problem relates in part to deficient activity at glutamate synapses, especially in the pre-frontal cortex. In many brain areas, dopamine inhibits glutamate release, or glutamate stimulates neurons that inhibit dopamine release. Therefore, increased dopamine would produce the same effects as decreased glutamate. The antipsychotic effects of drugs that block dopamine are compatible with either the excess-dopamine hypothesis or the deficient-glutamate hypothesis.

Schizophrenia is associated with lower than normal release of glutamate and fewer than normal receptors in the prefrontal cortex and hippocampus (Akbarian et al., 1995; Ibrahim et al., 2000; Tsai et al., 1995). Similar abnormalities occur in people known to be at high risk for developing schizophrenia, because of their family background and early behaviors (Valli et al., 2011). Mice with a deficiency of glutamate receptors show some abnormal behaviors, including increased anxiety, impaired memory, and impaired social behaviors (Belforte et al., 2010).

Further support for the glutamate hypothesis comes from the effects of **phencyclidine (PCP)** ("angel dust"), a drug that inhibits the NMDA glutamate receptors. At low doses, it produces intoxication and slurred speech. At larger doses, it produces both positive and negative symptoms of schizophrenia, including hallucinations, thought disorder, loss of emotions, and memory loss. PCP is an interesting model for schizophrenia in other regards also (Farber, Newcomer, & Olney, 1999; Olney & Farber, 1995):

- PCP and the related drug *ketamine* produce little if any psychotic response in preadolescents. Just as the symptoms of schizophrenia usually begin to emerge well after puberty, so do the psychotic effects of PCP and ketamine.
 - LSD, amphetamine, and cocaine produce temporary schizophrenic symptoms in almost anyone, and the effects are not much worse in people with a history of schizophrenia than in anyone else. However, PCP produces severe effects for someone who has recovered from schizophrenia, including a long-lasting relapse.

It might seem that the best test of the glutamate hypothesis would be to administer glutamate itself. However, recall from Chapter 5 that strokes kill neurons by overstimulating glutamate synapses. Increasing overall brain glutamate would be risky. However, drugs that stimulate particular kinds of metabotropic glutamate receptors have shown much promise in treating schizophrenia (González-Maeso et al., 2008; Patil et al., 2007).

Furthermore, the NMDA glutamate receptor has a primary site that is activated by glutamate and a secondary site that is activated by glycine (Figure 15.17). Glycine by itself does not activate the receptor, but it increases the effectiveness of glutamate. Thus, an increase in glycine can increase the activity at NMDA synapses without overstimulating glutamate throughout the brain. Although glycine is not an effective an-

STOP & CHECK

- 23.** What drugs induce mainly the positive symptoms of schizophrenia? What drug can induce both positive and negative symptoms?

- 24.** Why are the effects of antipsychotic drugs equally compatible with the dopamine hypothesis and the glutamate hypothesis?

ANSWERS

23. Repeated use of amphetamine, cocaine, or LSD increases positive symptoms, such as hallucinations and delusions. Phenylcyclidine induces both positive and negative symptoms. **24.** Dopamine inhibits glutamate receptors in many areas, and glutamate stimulates neurons that inhibit dopamine. Therefore, the effects of increasing dopamine are similar to those of decreas-

New Drugs

The brain has several dopamine pathways with different functions. The drugs that block dopamine synapses produce their benefits by acting on neurons in the **mesolimbocortical system**, a set of neurons that project from the midbrain tegmentum to the limbic system. However, the drugs also block dopamine neurons in the *mesostriatal system* that projects to the basal ganglia (Figure 15.18). The effect on the basal ganglia produces **tardive dyskinesia** (TARD-eev dis-kih-NEE-zhee-uh), characterized by tremors and other involuntary movements that develop gradually and to varying degrees among different patients (Kiriakakis, Bhatia, Quinn, & Marsden, 1998).

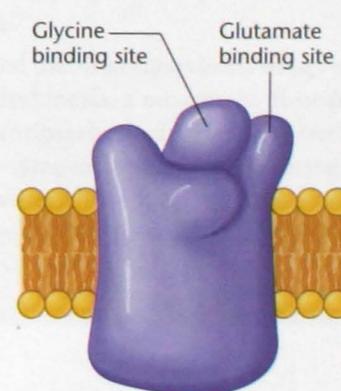


FIGURE 15.17 An NMDA glutamate receptor

NMDA glutamate receptors have a primary binding site for glutamate and a secondary binding site for glycine. Glycine increases the effect of glutamate. (© Cengage Learning 2013)

- 23.** The ability of traditional antipsychotic drugs to relieve schizophrenia correlates strongly with what effect on neurotransmitters?

ANSWER

22. their ability to relieve schizophrenia symptoms
strongly with how well they block activity at dopamine
synapses.

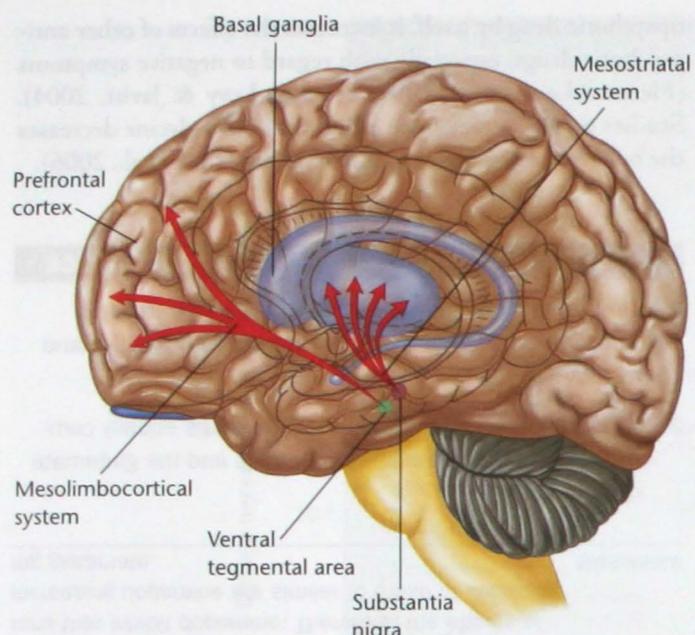


FIGURE 15.18 Two major dopamine pathways

Overactivity of the mesolimbocortical system is linked to the symptoms of schizophrenia. The path to the basal ganglia is associated with tardive dyskinesia, a movement disorder. (Adapted from Valzelli, 1980)

Once tardive dyskinesia emerges, it can last long after someone quits the drug (Kiriakakis et al., 1998). Consequently, the best strategy is to prevent it from starting. Certain new drugs called **second-generation antipsychotics**, or atypical antipsychotics, alleviate schizophrenia without producing movement problems (Figure 15.19). The most common of these drugs are clozapine, amisulpride, risperidone, olanzapine, and aripiprazole. They are more effective than older drugs at treating the negative symptoms of schizophrenia, and they are now used more widely (J. M. Davis, Chen, & Glick, 2003; Edlinger et al., 2005). Unfortunately, although

they avoid tardive dyskinesia, they produce other side effects, including weight gain and impairment of the immune system. All things considered, the atypical antipsychotics do not improve overall quality of life more than the older drugs (Crossley & Constante, 2010; P. B. Jones et al., 2006).

Compared to drugs like haloperidol, the second-generation antipsychotics have less effect on dopamine type D₂ receptors but more strongly antagonize serotonin type 5-HT₂ receptors (Kapur et al., 2000; Meltzer, Matsubara, & Lee, 1989; Mrzljak et al., 1996; Roth, Willins, Kristiansen, & Kroese, 1999). They also increase the release of glutamate (Melone et al., 2001). In short, schizophrenia is neither a one-gene disorder nor a one-neurotransmitter disorder.

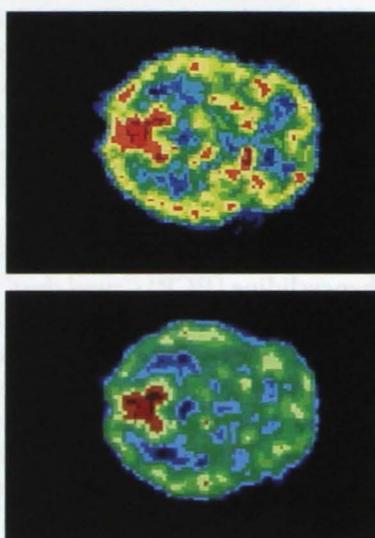


FIGURE 15.19 PET scans of a patient with schizophrenia

These PET scans of a patient with schizophrenia (a) taking clozapine and (b) during a period off the drug demonstrate that clozapine increases brain activity in many brain areas. Red indicates the highest activity, followed by yellow, green, and blue. (Hank Morgan/Science Source/Photo Researchers)

MODULE 15.2 ■ IN CLOSING

Many Remaining Mysteries

A great deal about abnormal psychology remains unknown. One of the most fundamental questions is whether it even makes sense to distinguish among different disorders. Some of the drugs originally approved for schizophrenia are often effective in relieving depression or bipolar disorder. Antidepressant drugs help relieve anxiety disorders. Drugs intended for bipolar disorder help many people with attention-deficit disorder. If the same treatments work for different disorders, maybe those disorders are not so different after all (Dean, 2011). Another major mystery is why concordance for schizophrenia in monozygotic twins is only about 50%. If they share their genes and presumably nearly the same environment, why isn't concordance nearly

SUMMARY

- Positive symptoms of schizophrenia (behaviors that are not present in most other people) include hallucinations, delusions, inappropriate emotions, bizarre behaviors, and thought disorder. 458
- Negative symptoms (normal behaviors absent that should be present) include deficits of social interaction, emotional expression, and speech. 458
- Studies of twins and adopted children imply a genetic predisposition to schizophrenia. However, the adoption studies do not distinguish between the roles of genetics and prenatal environment. 460
- So far, researchers have not located any gene that is strongly linked with schizophrenia in general. A promising hypothesis is that schizophrenia results from new mutations or deletions of any of the hundreds of genes that are important for brain development. 461
- According to the neurodevelopmental hypothesis, either genes or difficulties early in life impair brain development in ways that increase vulnerability to later insults and predispose to behavioral abnormalities beginning in early adulthood. 462
- The probability of schizophrenia is slightly higher than average for those who were subjected to difficulties before or at the time of birth or during early infancy. 462
- Some people with schizophrenia show mild abnormalities of brain development, especially in the temporal and frontal lobes. They also show cognitive deficits that make sense if their frontal and temporal lobes are less than fully functional. 463
- Parts of the prefrontal cortex are very slow to mature. It is plausible that early disruption of those areas might produce behavioral symptoms that become manifest as schizophrenia in young adults. 465
- According to the dopamine hypothesis, schizophrenia is due to excess dopamine activity. Drugs that block dopamine synapses reduce the positive symptoms of schizophrenia, and drugs that increase dopamine activity induce the positive symptoms. 465
- According to the glutamate hypothesis, part of the problem is deficient glutamate activity. Phencyclidine, which blocks NMDA glutamate synapses, produces both positive and negative symptoms of schizophrenia, especially in people predisposed to schizophrenia. 467
- Prolonged use of antipsychotic drugs may produce tardive dyskinesia, a movement disorder. Second-generation antipsychotic drugs relieve both positive and negative symptoms without producing tardive dyskinesia. However, these drugs apparently do not improve overall quality of life any better than the original drugs do. 467

100%? Also, why are the treatments for both depression and schizophrenia highly successful for some people and not at all for others? Perhaps you can name additional puzzles.

Research is a little like reading a good mystery novel that presents a mixture of important clues and irrelevant information. In research on schizophrenia, we have an enormous amount of information, but also major gaps and occasional points that don't seem to fit. The final chapter of our mystery novel on schizophrenia isn't complete. However, although researchers have not yet solved the mystery, it should also be clear that they have made progress. It will be fascinating to see what develops in future research.

KEY TERMS

Terms are defined in the module on the page number indicated. They're also presented in alphabetical order with definitions in the book's Subject Index/Glossary, which begins on page 567. Interactive flashcards and crossword puzzles are among the online resources available to help you learn these terms and the concepts they represent.

antipsychotic (neuroleptic) drugs	465	glutamate hypothesis of schizophrenia	467	schizophrenia	458
butyrophenones	465	hallucinations	458	season-of-birth effect	462
chlorpromazine	460	mesolimbocortical system	467	second-generation antipsychotics	468
concordance	465	negative symptoms	458	substance-induced psychotic disorder	466
delusions	458	neurodevelopmental hypothesis	462	tardive dyskinesia	467
differential diagnosis	459	phencyclidine (PCP)	467		
<i>DISC1</i>	461	phenothiazines	465		
dopamine hypothesis of schizophrenia	465	positive symptoms	458		

THOUGHT QUESTION

On average, people who use much marijuana are more likely than others to develop schizophrenia. However, over the last several decades, the use of marijuana has increased substantially

while the prevalence of schizophrenia has remained steady or decreased. What would be a reasonable conclusion about the relationship between marijuana use and schizophrenia?