Chapter 13

Schizophrenia and Other Psychotic Disorders

Learning Objectives

13.1 Describe the prevalence of schizophrenia and who is most affected.

13.2 Identify the symptoms of schizophrenia as described in *DSM-5*.

13.3 List four different types of psychotic disorders and state one way in which each is different from schizophrenia.

13.4 Explain the genetic and biological risk and causal factors associated with schizophrenia.

13.5 Discuss how the brain is affected in schizophrenia.

13.6 Explain the psychosocial and cultural factors associated with schizophrenia.

13.7 Describe the clinical outcome of schizophrenia and how is it treated, noting the advantages and disadvantages associated with the use of antipsychotic medications.

Emilio: "Eating Wires and Lighting Fires"

Emilio is a 40-year-old man who looks 10 years younger. He is brought to the hospital, his 12th hospitalization, by his mother because she is afraid of him. He is dressed in a ragged overcoat, bedroom slippers, and a baseball cap, and he wears several medals around his neck. His affect ranges from anger at his mother ("She feeds me shit . . . what comes out of other people's rectums") to a giggling, obsequious seductiveness toward the interviewer. His speech and manner have a childlike quality, and he walks with a mincing step and exaggerated hip movements. His mother reports that he stopped taking his medication about a month ago and has since begun to hear voices and to look and act more bizarrely. When asked what he has been doing, he says "Eating wires and lighting fires." His spontaneous speech is often incoherent and marked by frequent rhyming and clang associations (where sounds, rather than meaningful relationships, govern word choice).

Emilio's first hospitalization occurred after he dropped out of school at age 16, and since that time he has never been able to attend school or hold a job. He has been treated with neuroleptics (medications used to treat schizophrenia) during his hospitalizations, but he doesn't continue to take his medications when he leaves, so he quickly becomes disorganized again. He lives with his elderly mother, but he sometimes disappears for several months at a time and is eventually picked up by the police as he wanders the streets. (Modified from Spitzer et al., 2002, pp. 189–190.)

The disorder that Emilio has is called schizophrenia. Schizophrenia is a severe disorder that is often associated with considerable impairments in functioning. This chapter describes the pieces of the schizophrenia puzzle through a description of both classic studies as well as the most recent research. Keep in mind from the outset that not all of the pieces or their presumed interconnections have been found, so our puzzle is far from being solved. As you read through this chapter you will learn just how complex and challenging this disorder is—not only for patients who suffer from it and for their families who try to care for them, but also for the clinicians who attempt to treat it and the researchers who are determined to understand it.

Schizophrenia

13.1 Describe the prevalence of schizophrenia and who is most affected.

Schizophrenia occurs in people from all cultures and from all walks of life. The disorder is characterized by an array of diverse symptoms, including extreme oddities in perception, thinking, action, sense of self, and manner of relating to others. However, the hallmark of schizophrenia is a significant loss of contact with reality, referred to as **psychosis**. Although the clinical presentation of schizophrenia differs from one patient to another, the case of Emilio is quite typical.

The internal suffering of the person with schizophrenia is often readily apparent, as are bizarre behavior and unusual appearance.

Origins of the Schizophrenia Construct

The first detailed clinical description of what we now recognize to be schizophrenia was offered in 1810 by John Haslam, the apothecary at the Bethlem Hospital in London, England. Haslam described the case of a patient who appears to have suffered from a variety of symptoms—including delusions—that are typical of schizophrenia (see Carpenter, 1989). Fifty years later, the Belgian psychiatrist Benedict Morel described the case of a 13-year-old boy who had formerly been the most brilliant pupil in his school but who gradually lost interest in his studies; became increasingly withdrawn, lethargic, reclusive, and quiet; and appeared to have forgotten everything he had learned. Morel thought the boy's intellectual, moral, and physical functions had deteriorated as a result of brain degeneration of hereditary origin. He used the term *démence précoce* (mental deterioration at an early age) to describe the condition and to distinguish it from the dementing disorders associated with old age.

It is the German psychiatrist Emil Kraepelin (1856–1926) who is best known for his careful description of what we now regard as schizophrenia. Kraepelin used the Latin version of Morel's term (*dementia praecox*) to refer to a group of conditions that all seemed to feature mental deterioration beginning early in life. Kraepelin, an astute observer of clinical phenomena, described the patient with dementia praecox as someone who "becomes suspicious of those around him, sees poison in his food, is pursued by the police, feels his body is being influenced, or thinks that he is going to be shot or that the neighbours are jeering at

him" (Kraepelin, 1896). Kraepelin also noted that the disorder was characterized by hallucinations, apathy and indifference, withdrawn behavior, and an incapacity for regular work.

It was a Swiss psychiatrist named Eugen Bleuler (1857–1939) who gave us the diagnostic term we still use today. In 1911, Bleuler used *schizophrenia* (from the Greek roots of *sxizo*, pronounced "schizo" and meaning "to split or crack," and *phren*, meaning "mind") because he believed the condition was characterized primarily by disorganization of thought processes, a lack of coherence between thought and emotion, and an inward orientation away (split off) from reality. Although the term is often thought to reflect a "Jekyll and Hyde" split personality, this is a major misconception. The splitting does not refer to multiple personalities (an entirely different form of disorder, now called dissociative identity disorder). Instead, in schizophrenia there is a split within the intellect, between the intellect and emotion, and between the intellect and external reality. Interestingly, the subtitle of Bleuler's monograph (Bleuler, 1911/1950) was "The Group of Schizophrenias," indicating that he believed this disorder was not a single diagnostic entity.

Epidemiology

The risk of developing schizophrenia over the course of one's lifetime is a little under 1 percent—actually around 0.7 percent (Saha et al., 2005). What this means is that approximately 1 out of every 140 people alive today who survive until at least age 55 will develop the disorder. Of course, a statistic like this does not mean that everyone has exactly the same risk. This is an average lifetime risk estimate. As we shall see later, some people (e.g., those who have a parent with schizophrenia) have a statistically higher risk of developing the disorder than do others (e.g., people who come from families where there has never been a case of schizophrenia).

There are also other groups of people who seem to have an especially high risk of developing schizophrenia. For example, people whose fathers were older (50 years or more) at the time of their birth have an elevated risk of developing schizophrenia when they grow up (Miller et al., 2011). Having a parent who works as a dry cleaner is also a risk factor (Perrin, Opler, et al., 2007). Rates of schizophrenia are also higher than expected in first- and second-generation immigrants, particularly those from black Caribbean and black African countries who live in majority white communities (Bourque et al., 2011; Matheson et al., 2014). Although the reasons for these differences are not well understood, they are of great interest to researchers.

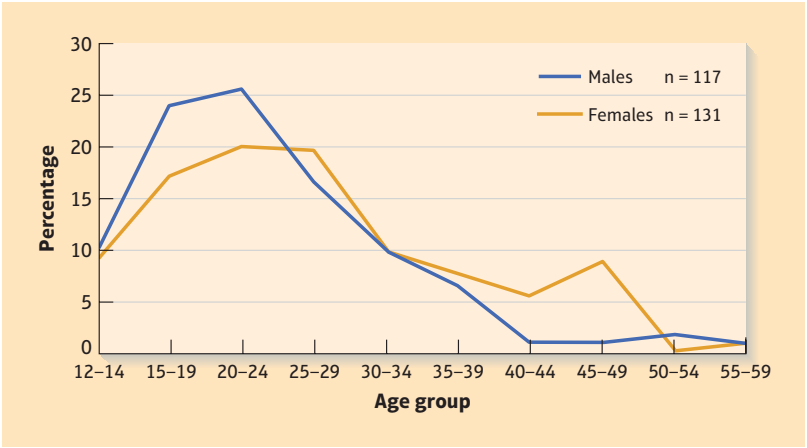
The vast majority of cases of schizophrenia begin in late adolescence and early adulthood, with 18 to 30 years of age being the peak time for the onset of the illness (Tandon et al., 2009). Although schizophrenia is sometimes found in children, such cases are rare (Green et al., 1992; McKenna et al., 1994). Schizophrenia can also have its initial onset in middle age or later, but again, this is not typical.

The characteristic age of onset of schizophrenia differs in men and women. In men, there is a peak in new cases of schizophrenia between ages 20 and 24. The incidence of schizophrenia in women peaks during the same age period, but the peak is less marked than it is for men (see Figure 13.1). After about age 35, the number of men developing schizophrenia falls markedly, whereas the number of women developing schizophrenia does not. Instead,

Figure 13.1 Onset of Schizophrenia

Age distribution of onset of schizophrenia (first sign of mental disorder) for men and women.

(Adapted from Haffner, H., et al. (1998). Causes and consequences of the gender difference in age at onset of schizophrenia. *Schizophrenia Bulletin*, *24*(1), 99–114.)



there is a second rise in new cases that begins around age 40, as well as a third spike in onset that occurs when women are in their early sixties (Abel et al., 2010).

Children whose fathers are older at the time of their birth have two to three times the normal risk of developing schizophrenia.

In addition to being more likely to have an early age of onset, males also tend to have a more severe form of schizophrenia (Leung & Chue, 2000). Brain-imaging studies show that schizophrenia-related anomalies of brain structure (discussed later) are more severe in male patients than they are in female patients. Gender-related differences in illness severity may also explain why schizophrenia is more common in males than it is in females. The male-to-female ratio is 1.4:1. So for every three men who develop the disorder, only two women do so (Aleman et al., 2003; Kirkbridge et al., 2006). If women have a less severe form of schizophrenia, and if they also have more symptoms of depression (see Leung & Chue, 2000), they may either not be diagnosed at all or else be diagnosed with other disorders, thus giving rise to the sex ratio imbalance.

What might explain the better clinical outcome of women with schizophrenia? One possibility is that female sex hormones play some protective role. When estrogen levels are low (as is true premenstrually) or are falling, psychotic symptoms in women with schizophrenia often get worse (Bergemann et al., 2007). The protective effect of estrogen may therefore help explain both the delayed onset of schizophrenia and the more favorable clinical course of the disorder in females. Declining levels of estrogen around menopause might also explain why late-onset schizophrenia is much more likely to strike women than men. There is some evidence that this late-onset pattern in women is associated with a more severe clinical presentation (Haffner et al., 1998).

in review

- What is schizophrenia characterized by? What is the hallmark of schizophrenia?
- What is the peak time for the onset of schizophrenia?
- Is schizophrenia the same thing as split personality?
- What is the prevalence of schizophrenia? What groups of people show lower or higher rates of schizophrenia than expected?
- How does the age of onset of schizophrenia vary by gender?
- How does gender influence the severity of schizophrenia? Why might this be?

Clinical Picture

13.2 Identify the symptoms of schizophrenia as described in *DSM-5*.

As we have mentioned earlier, the *DSM* is a work in progress. Diagnostic criteria are not fixed and immutable but instead change subtly over time as new research findings become available. We show the current *DSM-5* criteria for the diagnosis of schizophrenia in the *DSM-5* box. These are broadly similar to those used in *DSM-IV-TR* and to the diagnostic criteria in the *ICD* (WHO, 2003), which is the diagnostic system used in Europe and other parts of the world. One change that occurred with *DSM-5* was the elimination of the requirement that only one other symptom had to be present if delusions were bizarre or if the auditory hallucinations were of a certain type.

In isolation, however, lists of symptoms convey little about the clinical essence of schizophrenia. In the sections that follow, we elaborate on the hallmark symptoms of this major form of psychotic disorder.

Delusions

A **delusion** is essentially an erroneous belief that is fixed and firmly held despite clear contradictory evidence. The word *delusion* comes from the Latin verb *ludere*, which means "to play." In essence, tricks are played on the mind. People with delusions believe things that others who share their social, religious, and cultural backgrounds do not believe. A delusion therefore involves a disturbance in the *content* of thought. Not all people who have delusions suffer from schizophrenia. However, delusions are common in schizophrenia, occurring in more than 90 percent of patients at some time during their illness (Cutting, 1995). In schizophrenia, certain types of delusions or false beliefs

DSM-5 *Criteria for. . .*

Schizophrenia

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):

1. Delusions.
2. Hallucinations.
3. Disorganized speech (e.g., frequent derailment or incoherence).
4. Grossly disorganized or catatonic behavior.
5. Negative symptoms (i.e., diminished emotional expression or avolition).

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

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are quite characteristic. Prominent among these are beliefs that one's thoughts, feelings, or actions are being controlled by external agents (made feelings or impulses), that one's private thoughts are being broadcast indiscriminately to others (thought broadcasting), that thoughts are being inserted into one's brain by some external agency (thought insertion), or that some external agency has robbed one of one's thoughts (thought withdrawal). Also common are delusions of reference, where some neutral environmental event (such as a television program or a song on the radio) is believed to have special and personal meaning intended only for the person. Other strange propositions, including delusions of bodily changes (e.g., bowels do not work) or removal of organs, are also not uncommon.

Sometimes delusions are not just isolated beliefs. Instead they become elaborated into a complex delusional system. The next case study provides an example of this. This material was printed on a flier and handed to one of the authors by a man who appeared to be in his 30s. Any errors of grammar are errors in the original flier.

The inner world of people with schizophrenia is often confused, punctuated by alien voices, paranoia, and illogical thoughts.

Are You Being Mind Controlled?

Are you being or were you mind controlled to do something very stupid? Twenty-five percent of our population have what is called electronic hearing. This 25 percent can hear a silent radio and do not hear it. You might be one. In hearing pitch the average person hears from zero to sixteen thousand cycles. Twenty-five percent can hear up to thirty thousand cycles. The silent radio can be heard by these high hearing frequency persons. The silent radio sounds the same as thoughts in their minds.

This silent radio tricks these persons into every crime imaginable. It tricks them into bad decisions, to quit jobs, to divorce, to run away, to be sheriff saled and any stupidity possible. The broadcasters over this silent radio are government, medical, psychiatrists, religious and educational. This is an enormous budget used to destroy the innocent and helpless. The media is scared to cover this up.

This minority, which can be in any ethnic or race, has lost all rights under law because the Russians do it everywhere. It is shocking to discover very large corporations and all colleges have mind control departments. If you and your family constantly make bad decisions and have ruinous problems, you probably are mind controlled. Every year these mind controlled people are going down the economic ladder as they cannot be trusted. No company knows when one will be selected as a guinea pig. Who could risk a sizeable work force of persons with electronic hearing for your competitor could easily wipe you out?

Hallucinations

A **hallucination** is a sensory experience that seems real to the person having it, but occurs in the absence of any external perceptual stimulus. This is quite different from an illusion, which is a misperception of a stimulus that actually exists. The word comes from the Latin verb *hallucinere* or *allucinere*, meaning to "wander in mind" or "idle talk." Hallucinations can occur in any sensory modality (auditory, visual, olfactory, tactile, or gustatory). However, auditory hallucinations (e.g., hearing voices) are by far the most common. In a sample recruited from seven different countries, auditory hallucinations were found in 75 percent of patients with schizophrenia (Bauer et al., 2011). In contrast, visual hallucinations were reported less frequently (39 percent of patients), and olfactory, tactile, and gustatory hallucinations were even more rare (1–7 percent). Even deaf people who are diagnosed with schizophrenia sometimes report auditory hallucinations (Aleman & Larøi, 2008). As the World Around Us box illustrates, hallucinations can even be induced in healthy people if they are under a lot of stress and drink a lot of caffeine.

Hallucinations often have relevance for the patient at some affective, conceptual, or behavioral level. Patients can become emotionally involved in their hallucinations, often incorporating them into their delusions. In some cases, patients may even act on their hallucinations and do what the voices tell them to do. People who consider themselves to be socially inferior tend to perceive the voices they hear as being more powerful than they are and to behave accordingly (Paulik, 2011).

In a highly informative study of the phenomenology of auditory hallucinations, Nayani and David (1996) interviewed 100 hallucinating patients and asked them a series of questions about their hallucinatory voices. The majority of patients (73 percent) reported that their voices usually spoke at a normal conversational volume. Hallucinated voices were often those of people known to the patient in real life, although sometimes unfamiliar voices or the voices of God or the Devil were heard. Most patients reported that they heard more than one voice and that their hallucinations were worse when they were alone. Most commonly, the hallucinated voices uttered rude and vulgar expletives or else were critical ("You are stupid"), bossy ("Get the milk"), or abusive ("Ugly bitch"), although some voices were pleasant and supportive ("My darling").

Hallucinations can even be induced in healthy people if they are under a lot of stress and drink a lot of caffeine.

Are patients who are hallucinating really hearing voices? Neuroimaging studies that compare hallucinating patients with nonhallucinating patients suggest that patients with speech hallucinations have a reduction in brain (gray matter) volume in the left hemisphere auditory and speech perception areas (Allen et al., 2008). Reduced brain volume in these areas could lead to a failure to correctly identify internally generated speech, erroneously tagging it as coming from an external source. PET and fMRI studies that have looked at activity in the brains of patients when they are actually experiencing auditory hallucinations provide further support for this idea. Rather than showing an increase of activity in areas of the brain involved in speech comprehension (e.g., Wernicke's area in the temporal lobe), neuroimaging studies reveal that hallucinating patients show increased activity in Broca's area—an area of the temporal lobe that is involved in speech production. In some cases, the pattern of brain activation that occurs when patients experience auditory hallucinations is very similar to that seen when healthy volunteers are asked to imagine that there is another person talking to them (Shergill et al., 2000). Indeed, if transcranial magnetic stimulation (in which a magnetic field passing through the skull temporarily disrupts activity in underlying brain areas) is used to reduce activity in speech production areas, hallucinating patients actually show a reduction in their auditory hallucinations (Hoffman et al., 2005). Such an approach could possibly have promise for the future as a novel form of treatment (Slotema et al., 2014). Overall, however, the research findings suggest that auditory hallucinations occur when patients misinterpret their own self-generated and verbally mediated thoughts (inner speech or self-talk) as coming from another source. Modern research approaches are thus supporting a very old idea: Auditory hallucinations are really a form of misperceived subvocal speech (Gould, 1949).

The World Around Us

Stress, Caffeine, and Hallucinations

Do you feel that you are under a lot of stress? Do you drink a lot of caffeinated beverages each day? If so, you may be interested in the findings from a recent study that was conducted using healthy volunteers who had no history of psychiatric disorders (Crowe et al., 2011). Ninety-two participants were recruited into what they believed was a study of auditory perception. As participants entered the testing room to begin the experiment, the song "White Christmas" by Bing Crosby was playing. After the song ended, participants were given headphones and asked to listen to white noise. They were told that the "White Christmas" song they had just heard might be embedded in the white noise at a subthreshold level. Every time they thought they heard a fragment of the song during the 3 minutes of white noise, participants were told to note this using a hand counter.

In reality, no sound fragments of "White Christmas" were embedded in the sound at all. Participants only heard white noise. However, those participants who reported that they had been under a high level of stress in the past year *and* who were high caffeine users (five or more drinks per day) reported hearing significantly more embedded song fragments than participants in the low-stress and low-caffeine group did. Moreover, it was the combination of high stress and high caffeine intake that was important. In participants who reported high stress but low caffeine intake or in participants who reported low stress but high caffeine intake, the number of false alarms or "hallucinations" (hearing a song fragment that was not there) was not elevated. The associations also remained when variables such as age, creativity, social desirability, mental imagery ability, and hallucination-proneness were taken into account.

Overall the results of this study demonstrate that, under certain conditions, the combination of high caffeine consumption and high stress can render normal people vulnerable to auditory hallucinations. Caffeine is known to increase how much cortisol is produced in response to a stressor. Caffeine consumption has also been found to correlate with hallucination proneness in other studies of healthy people (Jones & Fernyhough, 2009). It is also important to note that patients with schizophrenia typically drink a great deal of coffee. During times of high stress, this might perhaps increase their risk of having an exacerbation in hallucinatory symptoms.

The combination of high stress levels and high caffeine intake is associated with hallucinations in psychiatrically healthy people.

Is it true that hallucinations are only found in people who have schizophrenia? If not, under what circumstances might hallucinations be induced?

Disorganized Speech

Delusions reflect a disorder of thought *content*, or in the ideas being expressed. Disorganized speech, on the other hand, is the external manifestation of a disorder in thought *form*. Basically, an affected person fails to make sense, despite seeming to using language in a conventional way and following the semantic and syntactic rules governing verbal communication. The failure is not attributable to low intelligence, poor education, or cultural deprivation. Years ago, Meehl (1962) aptly referred to the process as one of "cognitive slippage"; others have referred to it as "derailment" or "loosening" of associations or, in its most extreme form, as "incoherence."

In disorganized speech, the words and word combinations sound communicative, but the listener is left with little or no understanding of the point the speaker is trying to make. In some cases, completely new, made-up words known as *neologisms* (literally, "new words") appear in the patient's speech. An example might be the word *detone*, which looks and sounds like a meaningful word but is a neologism. *Formal thought disorder* (a term clinicians use to refer to problems in the way that disorganized thought is expressed in disorganized speech) is well illustrated in the following example. It is taken from a letter written by a man with schizophrenia and addressed to Queen Beatrix of the Netherlands.

Disorganized Speech: A Letter to Queen Beatrix

I have also "killed" my ex-wife, [name], in a 2.5 to 3.0 hours sex bout in Devon Pennsylvania in 1976, while two Pitcairns were residing in my next room closet, hearing the event. Enclosed, please find my urology report, indicating that my male genitals, specifically my penis, are within normal size and that I'm capable of normal intercourse with any woman, signed by Dr. [name], a urologist and surgeon who performed a circumcision on me in 1982. Conclusion: I cannot be a nincompoop in a physical sense (unless Society would feed me chemicals for my picture in the nincompoop book).

Disorganized Behavior

Disorganized behavior can show itself in a variety of ways. Goal-directed activity is almost universally disrupted in schizophrenia. The impairment occurs in areas of routine daily functioning, such as work, social relations, and self-care, to the extent that observers note that the person is not himself or herself anymore. For example, the person may no longer maintain minimal standards of personal hygiene or may exhibit a profound disregard of personal safety and health. In other cases, grossly disorganized behavior appears as silliness or unusual dress (e.g., wearing an overcoat, scarf, and gloves on a hot summer day). Many researchers attribute these disruptions of "executive" behavior to impairment in the functioning of the prefrontal region of the cerebral cortex.

Catatonia is an even more striking behavioral disturbance. The patient with catatonia may show a virtual absence of all movement and speech and be in what is called a *catatonic stupor*. At other times, the patient may hold an unusual posture for an extended period of time without any seeming discomfort.

A person with catatonia may maintain an odd position for minutes or even hours.

Negative Symptoms

Since the days of Bleuler, two general symptom patterns, or syndromes, of schizophrenia have been differentiated. These are referred to as positive- and negative-syndrome schizophrenia. Researchers began to highlight the difference between positive and negative symptoms in the 1980s (Andreasen, 1985) and this distinction is still relevant today.

Positive symptoms are those that reflect an excess or distortion in a normal repertoire of behavior and experience, such as delusions and hallucinations. Disorganized thinking (as revealed by disorganized speech) is also thought of in this way. **Negative symptoms**, by contrast, reflect an absence or deficit of behaviors that are normally present.

Current thinking is that negative symptoms fall into two broad domains (Barch, 2013; Kring et al., 2013). One domain involves reduced expressive behavior—either in voice, facial expression, gestures or speech. This may show itself in the form of **blunted affect** or **flat affect** or in **alogia**, which means very little speech. The other domain concerns reductions in motivation or in the experience of pleasure. The inability to initiate or persist in goal-directed activity is called **avolition**. For example, the patient may sit for long periods of time staring into space or watching TV with little interest in any outside work or social activities. Diminished ability to experience pleasure is called *anhedonia*.

Positive, negative, and disorganized symptoms can co-occur in the same patient. This woman appears to exhibit marked social withdrawal (a negative symptom) in addition to showing bizarre behavior (a disorganized symptom).

Although most patients exhibit both positive and negative symptoms during the course of their disorders, the presence of negative symptoms in the clinical picture is not a good sign for the patient's future outcome (e.g., Malla & Payne, 2005; Milev et al., 2005).

Even though patients with negative symptoms may seem emotionally unexpressive, how they appear and how they are feeling are two different things. In an important early study, Kring and Neale (1996) studied unmedicated male patients with schizophrenia while they were watching film clips. Three different types of film clips were used, the scenes in them being very positive, very negative, or neutral in terms of the emotions they were designed to elicit in the viewers. Videotapes of how the patients looked while they were watching the films were then coded by trained raters. As might be expected, the patients with schizophrenia showed less facial expressiveness than a group of healthy controls.

What *was* surprising was that when the patients were asked about their emotional experiences during the films, they reported as many emotional feelings as the controls—and sometimes slightly more. Measures of autonomic

arousal also showed that when they were watching the films, the patients exhibited more physiological reactivity than the controls did. Although the original research used only male patients, a recent study that includes women with schizophrenia has replicated the results about diminished emotional expression (Mote et al., 2014). What the findings suggest, therefore, is that even though patients with schizophrenia may sometimes appear emotionally unexpressive, they are nonetheless experiencing plenty of emotion.

Subtypes of Schizophrenia

There is a great deal of heterogeneity in the presentation of schizophrenia, and patients with this disorder often look quite different clinically. In consideration of this, the *DSM-IV-TR* recognized several subtypes of schizophrenia. The most clinically meaningful of these were **paranoid schizophrenia** (where the clinical picture is dominated by absurd and illogical beliefs that are often highly elaborated and organized into a coherent, though delusional, framework), **disorganized schizophrenia** (characterized by disorganized speech, disorganized behavior, and flat or inappropriate affect), and **catatonic schizophrenia** (which involves pronounced motor signs that reflect great excitement or stupor). Unfortunately, research using the subtyping approach did not yield major insights into the etiology or treatment of the disorder. Reflecting this, subtypes of schizophrenia are no longer included in *DSM-5*.

in review

- What are the major symptoms of schizophrenia?
- How is a hallucination different from a delusion?
- Explain the differences among positive, negative, and disorganized symptoms.
- Why were the subtypes of schizophrenia not included in *DSM-5*?

Other Psychotic Disorders

13.3 List four different types of psychotic disorders and state one way in which each is different from schizophrenia.

Schizophrenia is a form of psychotic disorder, but it is not the only one. There are a number of other types of psychotic disorders, such as schizoaffective disorder, schizophreniform disorder, delusional disorder, and brief psychotic disorder.

Schizoaffective Disorder

The *DSM-5* recognizes a diagnostic category called **schizoaffective disorder** (see the *DSM-5* box for diagnostic criteria). This diagnosis is conceptually something of a hybrid, in that it is used to describe people who have features of schizophrenia and severe mood disorder. In other words, the person not only has psychotic symptoms that meet criteria for schizophrenia but also has marked changes in mood for a substantial amount of time. Because mood disorders can be unipolar or bipolar in type, these are recognized as subtypes of schizoaffective disorder.

The reliability of schizoaffective disorder has tended to be quite poor, and clinicians often do not agree about who meets the criteria for the diagnosis (Maj et al., 2000; Vollmer-Larsen et al., 2006). In an effort to improve this, *DSM-5* specifies that mood symptoms have to meet criteria for a full major mood episode and also have to be present for more than 50 percent of the total duration of the illness. This clarification should help improve the reliability of this diagnosis and possibly also decrease the number of people who receive it.

DSM-5 *Criteria for. . .*

Schizoaffective Disorder

A. An uninterrupted period of illness during which there is a major mood episode (major depressive or manic) concurrent with Criterion A of schizophrenia.
Note: The major depressive episode must include Criterion A1: Depressed mood.

B. Delusions or hallucinations for 2 or more weeks in the absence of a major mood episode (depressive or manic) during the lifetime duration of the illness.

C. Symptoms that meet criteria for a major mood episode are present for the majority of the total duration of the active and residual portions of the illness.

D. The disturbance is not attributable to the effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

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In general, the prognosis for patients diagnosed with schizoaffective disorder is somewhere between that of patients with schizophrenia and that of patients with mood disorders (Walker et al., 2004). Research suggests that the long-term (10-year) outcome is much better for patients with schizoaffective disorder than it is for patients with schizophrenia (Harrow et al., 2000).

Schizophreniform Disorder

Schizophreniform disorder is a category reserved for schizophrenia-like psychoses that last at least a month but do not last for 6 months and so do not warrant a diagnosis of schizophrenia (see the *DSM-5* box for diagnostic criteria). It may include any of the symptoms described in the

DSM-5 *Criteria for. . .*

Schizophreniform Disorder

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):

1. Delusions.
2. Hallucinations.
3. Disorganized speech (e.g., frequent derailment or incoherence).
4. Grossly disorganized or catatonic behavior.
5. Negative symptoms (i.e., diminished emotional expression or avolition).

B. An episode of the disorder lasts at least 1 month but less than 6 months. When the diagnosis must be made without waiting for recovery, it should be qualified as "provisional."

C. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either (1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or (2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.

D. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

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preceding sections. Because of the possibility of an early and lasting remission after a first psychotic breakdown, the prognosis for schizophreniform disorder is better than that for established forms of schizophrenia.

Delusional Disorder

Patients with **delusional disorder**, like many people with schizophrenia, hold beliefs that are considered false and absurd by those around them. Unlike individuals with schizophrenia, however, people given the diagnosis of delusional disorder may otherwise behave quite normally. Their behavior does not show the gross disorganization and performance deficiencies characteristic of schizophrenia, and general behavioral deterioration is rarely observed in this disorder, even when it proves chronic (see the *DSM-5* box for criteria for delusional disorder). One interesting subtype of delusional disorder is *erotomania*. Here, the theme of the delusion involves great love for a person, usually of higher status. Some evidence suggests that a significant proportion of female stalkers are diagnosed with erotomania (Purcell et al., 2001; West & Friedman, 2008).

Brief Psychotic Disorder

Brief psychotic disorder is exactly what its name suggests. It involves the sudden onset of psychotic symptoms or disorganized speech or catatonic behavior. Even though there is often great emotional turmoil, the episode usually lasts only a matter of days (too short to warrant a diagnosis of schizophreniform disorder). After this, the person returns to his or her former level of functioning and may never have another episode again (see the *DSM-5* box for criteria for brief psychotic disorder). Cases of brief psychotic disorder are infrequently seen in clinical settings, perhaps because they remit so quickly. Brief psychotic disorder is often triggered by stress, as illustrated in the following case.

DSM-5 *Criteria for. . .*

Delusional Disorder

A. The presence of one (or more) delusions with a duration of 1 month or longer.

B. Criterion A for schizophrenia has never been met.
Note: Hallucinations, if present, are not prominent and are related to the delusional theme (e.g., the sensation of being infested with insects associated with delusions of infestation).

C. Apart from the impact of the delusion(s) or its ramifications, functioning is not markedly impaired, and behavior is not obviously bizarre or odd.

D. If manic or major depressive episodes have occurred, these have been brief relative to the duration of the delusional periods.

E. The disturbance is not attributable to the physiological effects of a substance or another medical condition and is not better explained by another mental disorder, such as body dysmorphic disorder or obsessive-compulsive disorder.

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DSM-5 *Criteria for. . .*

Brief Psychotic Disorder

A. Presence of one (or more) of the following symptoms. At least one of these must be (1), (2), or (3):

1. Delusions.
2. Hallucinations.
3. Disorganized speech (e.g., frequent derailment or incoherence).
4. Grossly disorganized or catatonic behavior.

Note: Do not include a symptom if it is a culturally sanctioned response.

B. Duration of an episode of the disturbance is at least 1 day but less than 1 month, with eventual full return to premorbid level of functioning.

C. The disturbance is not better explained by major depressive or bipolar disorder with psychotic features or another psychotic disorder such as schizophrenia or catatonia, and is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

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Four Days of Symptoms and Rapid Recovery

Ronald was 32 years old and had worked successfully as a lawyer for 6 years. He was married with two young children and he had many close friends. One day he returned home early from work and was shocked to find his wife in bed with his best friend. His initial reaction was anger, followed by depression. However, within 2 days he began to hear voices that called his name and that said, "Love, love, love." Ronald began to express odd ideas, speaking of fusing with God and dispensing peace on Earth. He also talked about needing to fight what he called the "giant conspiracy." During this time his affect was flat and he spoke in a slow and distinct manner. Ronald was admitted to hospital and was given medication. He and his wife also began marital therapy. Ronald showed rapid improvement of his symptoms and within 5 days of the onset of his initial symptoms he was back at work again. (Based on Janowsky et al., 1987.)

in review

- In what ways are schizophrenia and schizoaffective disorder different?
- How will the change to the criteria for schizoaffective disorder in *DSM-5* improve the reliability of this diagnosis?
- What are the major differences between schizophreniform disorder and brief psychotic disorder?

Genetic and Biological Factors

13.4 Explain the genetic and biological risk and causal factors associated with schizophrenia.

What causes schizophrenia? Despite enormous efforts by researchers, this question still defies a simple answer. In the sections that follow, we discuss what is currently known about the etiology of schizophrenia. What is clear is that no one factor can fully explain why schizophrenia develops. The old dichotomy of nature versus nurture is as misleading as it is simplistic. Psychiatric disorders are not the result of a single genetic switch being flipped. Rather, a complex interplay between genetic and environmental factors is responsible.

Genetic Factors

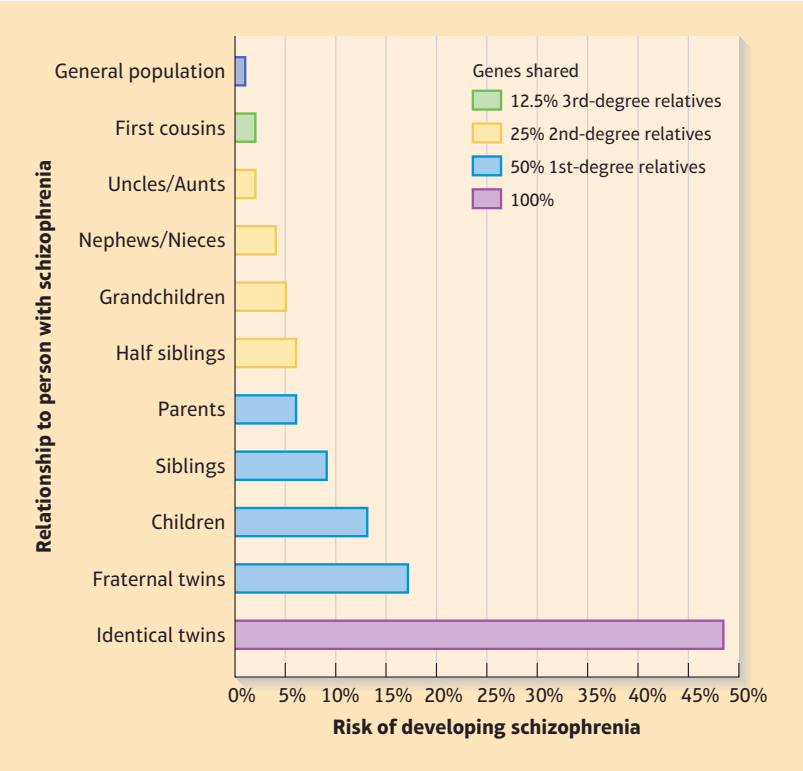
It has long been known that disorders of the schizophrenia type are "familial" and tend to "run in families." There is overwhelming evidence for higher-than-expected rates of schizophrenia among biological relatives of *index* cases; that is, the diagnosed group of people who provide the starting point for inquiry (also called *probands*). Figure 13.2 shows the percentage risk of developing schizophrenia given a specific genetic relationship with someone who has the disorder. As you can see, there is a strong association between the closeness of the blood relationship (i.e., level of gene sharing or consanguinity) and the risk for developing the disorder. For example, the prevalence of schizophrenia in the first-degree relatives (parents, siblings, and offspring) of a proband with schizophrenia is about 10 percent. For second-degree relatives who share only 25 percent of their genes with the proband (e.g., half-siblings, aunts, uncles, nieces, nephews, and grandchildren), the lifetime prevalence of schizophrenia is closer to 3 percent.

Of course, just because something runs in families does not automatically implicate genetic factors. The terms *familial* and *genetic* are not synonymous, and a disorder can run in a family for nongenetic reasons (if I am obese and my dog is also obese, the reasons for this are clearly not genetic!). As we have repeatedly emphasized, the interpretation of familial concordance patterns is never completely straightforward, in part because of the strong relationship between the sharing of genes and the sharing of the environments in which those genes express themselves. Although they are indispensable in providing a starting point for researchers, family studies cannot, by themselves, tell us why a disorder runs in families. To disentangle the contributions of genes and environment, we need twin and adoption studies.

Figure 13.2 Risk of Developing Schizophrenia by Genetic Relationship

Lifetime age-adjusted, averaged risks for the development of schizophrenia-related psychoses in classes of relatives differing in their degree of genetic relatedness.

(Compiled from family and twin studies in European populations between 1920 and 1987. From Gottesman, I. I. (1991). *Schizophrenia Genesis: The Origins of Madness* (p. 96). Copyright © 1991 by Irving I. Gottesman. Used with permission of W. H. Freeman and Company/Worth Publishers.)



TWIN STUDIES We discussed twin studies in general in Chapter 3 and again more specifically in relation to anxiety and mood disorders. As with the mood disorders, schizophrenia concordance rates for identical twins are routinely and consistently found to be significantly higher than those for fraternal twins or ordinary siblings. The most famous case of concordance for schizophrenia involves the Genain quadruplets. Their story is summarized in the World Around Us box.

Although being a twin does not increase one's risk for developing schizophrenia (the incidence of schizophrenia among twins is no greater than it is for the general population), study after study has shown a higher concordance for schizophrenia among identical, or monozygotic (MZ), twins than among people related in any other way, including fraternal, or dizygotic (DZ), twins.

E. Fuller Torrey is a noted schizophrenia researcher who has a sister with the disorder. He and his colleagues (1994) published a review of the major literature worldwide on twin studies of schizophrenia. The overall pairwise concordance rate is 28 percent in MZ twins and 6 percent in DZ twins. This suggests that a reduction in shared genes from 100 percent to 50 percent reduces the risk of schizophrenia by nearly 80 percent. Also note that sharing 50 percent of one's genes with a co-twin with schizophrenia is associated with a lifetime risk for schizophrenia of 6 percent. Although this is low in absolute terms, it is markedly higher than the baseline risk of less than 1 percent found in the general population.

If schizophrenia were exclusively a genetic disorder, the concordance rate for identical twins would, of course, be 100 percent. Although MZ concordance rates vary from one twin study to another, and although some researchers report higher rates than the 28 percent reported by Torrey and colleagues (1994), they are never even close to 100 percent. Two conclusions can therefore be drawn: First, genes undoubtedly play a role in causing schizophrenia. Second, genes themselves are not the whole story. Twin studies provide some of the most solid evidence that the environment plays an important role in the development of schizophrenia. But why one MZ twin should develop schizophrenia when his or her co-twin does not is a fascinating question.

The World Around Us

The Genain Quadruplets

The Genain quadruplets, born sometime in the early 1930s, were rare MZ quadruplets who each developed schizophrenia, an outcome that would be expected to occur by chance only once in approximately 1.5 billion births. The genetically identical girls, given the pseudonym *Genain* (from the Greek for "dreadful gene"), were hospitalized at the National Institute of Mental Health in the mid-1950s and studied intensively by lead researcher David Rosenthal (see Rosenthal, 1963; see also Mirsky & Quinn, 1988). Rosenthal also selected first names for the girls using the initials of the institution, NIMH. Accordingly, the women are known to us as Nora (the firstborn), Iris, Myra, and Hester. They are all concordant for schizophrenia. However, they are discordant with regard to the severity of their illnesses.

Hester has been the most severely ill Genain. She was born last and had the lowest birth weight. Hester was always the slowest to develop, and was removed from school after 11th grade. She has experienced chronic and unremitting severe symptoms from the age of 18 and has never held a job outside the home. Testing at NIMH revealed that, like Nora, Hester showed a great deal of neurocognitive impairment.

Nora was always considered by the family to be the best of the four girls. She had the highest IQ and was the first to get a job. Nonetheless, after she was hospitalized at the age of 22 with hallucinations, delusions, and withdrawal, she had a long history of hospitalizations and has never been able to live independently or hold a job for an extended period of time.

In contrast, third-born Myra, despite having some problems in her 20s (when she was questionably diagnosed as having schizophrenia), does not appear to have experienced delusions and paranoia until her mid-40s. Myra was the only one of the Genains to marry and have children and her clinical picture is more suggestive of schizoaffective disorder (a blend of psychotic symptoms and mood symptoms). Although she was never psychiatrically well by any definition, Myra was able to go off medications and eventually went into remission.

Finally, there is Iris. Like Nora, Iris had her first psychiatric hospitalization at age 22. She spent 12 years in a state hospital and suffered from hallucinations, delusions, and motor abnormalities. Although neurocognitive testing did not reveal any obvious brain disturbance, she clearly has a severe form of schizophrenia.

Why do these identical quadruplets not have identical illnesses? We do not know. Did Nora and Hester, being born first and last, experience more traumatic birth complications? Did Iris do less well than might have been expected from her neurocognitive test results because her parents insisted on treating the quads as though they were two sets of twins—a superior and talented set consisting of Nora and Myra, and an inferior, problematic set consisting of Iris and Hester? Did being paired with Hester somehow compromise Iris's development? Did Myra do so well (relatively) because she was the most favored and because she did not sustain any brain damage?

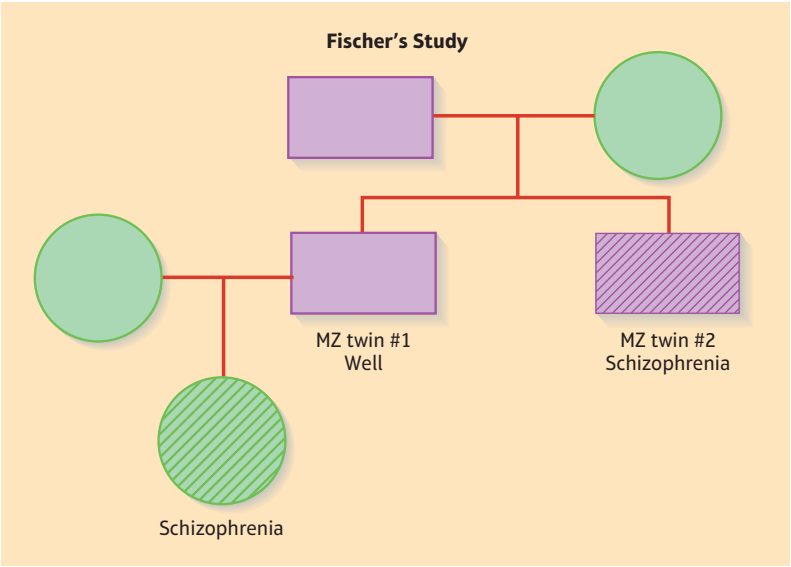
And why did the quadruplets develop schizophrenia at all? It is very likely that there was a family history of the disorder. Mr. Genain's mother (the girls' grandmother) had a nervous breakdown in her teens and appears to have had some symptoms of paranoid schizophrenia. The family environment was also far from healthy and may have provided the stress that acted on the quadruplets' genetic predispositions to induce full-blown illness. Mr. Genain was a very disturbed man who spent most of his time drinking and expressing his various fears and obsessions to his family. He imposed extreme restrictions and surveillance on the girls until the time of their breakdowns. He was sexually promiscuous and was reported to have sexually molested at least two of his daughters. Mrs. Genain seems to have ignored the sexual exploitation occurring in the home. In short, nothing about the family environment can be considered to have been normal.

What insights about schizophrenia do we get from the fact that the Genain quadruplets (who were all identical genetically) did not have identical forms of the illness?

A great deal of research attention is now being directed at studying people with a known genetic liability for schizophrenia. Historically, the most important subjects to study in this regard have been MZ twins who are discordant for schizophrenia. This investigative strategy was pioneered many years ago by Fischer (1971, 1973) in an ingenious study. Fischer reasoned that genetic influences, if present, would be just as likely to show up in the offspring of the twins without schizophrenia in discordant pairs (see Figure 13.3) as they would be to show up in the offspring of the twins with schizophrenia (because they share all their genes in common). And, in a search of official records in Denmark, Fischer found exactly that. Subsequent to this, in a follow-up of Fischer's subjects, Gottesman and Bertelson (1989) reported an ***age-corrected incidence rate*** for schizophrenia of 17.4 percent for the offspring of the MZ twins without schizophrenia (i.e., the well MZ twins). This rate, which far exceeds normal expectancy, was not significantly different from that for offspring of the twins with schizophrenia in discordant pairs or from that for offspring of DZ twins with schizophrenia. Assuming that exposure to an aunt or uncle with schizophrenia would play a limited role in the development of the same illness in their nieces or nephews, these results lend impressive support to the genetic hypothesis. They also, as the authors note, indicate that a predisposition to schizophrenia may remain "unexpressed" (as in the twins without schizophrenia in discordant pairs) unless "released" by unknown environmental factors.

Figure 13.3 Fischer's Study

Because MZ twins have identical genes, the children of the well twin will have an elevated risk of schizophrenia even if their parent did not suffer from the disorder.



Research Close-Up

Age-Corrected Incidence Rate

Incidence is the number of new cases that develop. An age-corrected incidence rate takes into account predicted breakdowns for subjects who are not yet beyond the age of risk for developing the disorder.

ADOPTION STUDIES One major assumption that twin studies make is that any differences found between MZ and DZ twins are attributable to genes. At the heart of this assumption is the idea that the environments of MZ twins are no more similar than the environments of DZ twins. But it is very reasonable to expect that, because MZ twins are identical (and always of the same gender), their environments will actually be more similar than the environments of DZ twins. To the extent that this is true, twin studies will overestimate the importance of genetic factors (because some similarities between MZ twins that actually occur for nongenetic reasons will be attributed to genetic factors). In some cases, of course, MZ twins go to a great deal of effort to try to be different from one another. The bottom line, however, is that the assumption that MZ and DZ twins have equally similar environments can create some problems when we try to interpret the findings of twin studies.

Several studies have attempted to overcome the shortcomings of the twin method in achieving a true separation of hereditary from environmental influences by using what is called the adoption strategy. Here, concordance rates for schizophrenia are compared for the biological and the adoptive relatives of people who have been adopted out of their biological families at an early age (preferably at birth) and have subsequently developed schizophrenia. If concordance is greater among the patients' biological rather than adoptive relatives, a hereditary influence is strongly suggested; the reverse pattern would argue for environmental causation.

The first study of this kind was conducted many years ago by Heston in 1966. Heston followed up 47 children who had been born to mothers who were in a state mental hospital suffering from schizophrenia. The children had been placed with relatives or into foster homes within 72 hours of their birth. In his follow-up study, Heston found that 16.6 percent of these children were later diagnosed with schizophrenia. In contrast, none of the 50 control children (selected from among residents of the same foster homes whose biological mothers did not have schizophrenia) developed schizophrenia. In addition to the greater probability of being diagnosed with schizophrenia, the offspring whose mothers had schizophrenia were also more likely to be diagnosed as mentally retarded, neurotic, or psychopathic (i.e., antisocial). They also had been involved more frequently in criminal activities and had spent more time in penal institutions. These findings are often taken to suggest that any genetic liability conveyed by the mothers is not specific to schizophrenia but also includes a liability for other forms of psychopathology. But we must be careful about drawing such a conclusion. Heston's study provided no information about psychopathology in the fathers of the children. We therefore cannot know to what extent some of the problems the children had were due to genetic liability conveyed by their fathers.

Heston's study began by identifying mothers with schizophrenia and then traced what had happened to their adopted-away offspring. An alternative approach involves locating adult patients with schizophrenia who were adopted early in life and then looking at rates of schizophrenia in their biological and adoptive relatives. A large-scale and multifaceted adoption study of this type was undertaken in Denmark, with Danish and American investigators working in collaboration (Kendler & Gruenberg, 1984; Kendler et al., 1994; Kety et al., 1978, 1994). As would be expected on the basis of a genetic model, the data showed a preponderance of schizophrenia and "schizophrenia-spectrum" problems (e.g.,

schizotypal and paranoid personality disorder) in the biological relatives of adoptees with schizophrenia. More specifically, 13.3 percent of the 105 biological relatives had schizophrenia or schizophrenia-spectrum disorders themselves. In contrast, only 1.3 percent of the 224 adoptive parents showed such problems.

THE QUALITY OF THE ADOPTIVE FAMILY The Danish adoption studies did not include independent assessments of the child-rearing adequacy of the adoptive families into which the index children (those who developed schizophrenia) and the control children (those who did not) had been placed. It remained for Tienari and colleagues (1987, 2000, 2004) to add this feature to their research design. The Finnish Adoptive Family Study of Schizophrenia, as it is known, followed up the adopted-away children of all women in Finland who were hospitalized for schizophrenia between 1960 and 1979. As they grew to adulthood, the functioning of these index children was compared with the functioning of a control sample of adoptees whose biological mothers were psychiatrically healthy. Over the course of a 21-year follow-up, the index adoptees developed more schizophrenia and schizophrenia-related disorders than did the controls (Tienari et al., 2000, 2003). What sets this study apart, however, is what it tells us about the interaction between genes and environment.

One measure of the family environment that the researchers looked at was communication deviance (Wahlberg et al., 1997). Communication deviance is a measure of how understandable and "easy to follow" the speech of a family member is. Vague, confusing, and unclear communication reflects high communication deviance. What Wahlberg and colleagues found was that it was the combination of genetic risk and high communication deviance in the adopted families that was problematic. Children who were at genetic risk and who lived in families where there was high communication deviance showed high levels of thought disorder at the time of the follow-up. In contrast, the control adoptees who had no genetic risk for schizophrenia showed no thought disorder, regardless of whether they were raised in a high- or a low-communication-deviance family. Perhaps what was most remarkable, though, was the outcome for the high-risk children who were raised by adopted families low in communication deviance. These children were healthier at follow-up than any of the other three groups! In other words, if they are raised in a benign environment, even children who are at genetic risk for schizophrenia appear to do very well.

Even if children are at genetic high risk for schizophrenia they are less likely to develop the disorder if they are raised in a healthy family environment.

Tienari and colleagues (2004) have provided further evidence of a genotype–environment interaction in schizophrenia. (If you are unsure what these terms mean, check back to Chapter 3.) Using interviews, the researchers first looked at the quality of the family environment in which the adopted children were raised. They then looked at what happened to the children who were raised in healthy versus dysfunctional families. The degree of adversity in the family environment predicted later problems in the adopted children. However, only those children who were raised in dysfunctional families *and* had high genetic risk for schizophrenia went on to develop schizophrenia-related disorders themselves. Children at high genetic risk who were raised in healthy family environments did not develop problems any more frequently than did children at low genetic risk.

These findings are important because they suggest that our genetic makeup may control how sensitive we are to certain aspects of our environments. If we have no genetic risk, certain kinds of environmental influences may not affect us very much. But if we have high genetic risk, we may be much more vulnerable to certain types of environmental risks such as high communication deviance or adverse family environments. Findings such as these also raise the exciting possibility that certain kinds of environments may protect people with a genetic susceptibility to schizophrenia from ever developing the illness.

In summary, these findings indicate a strong interaction between genetic vulnerability and an unfavorable family environment in the causal pathway leading to schizophrenia. Of course, it could be argued that the children who went on to develop problems caused the disorganization of their adoptive families. However, there is little support for this alternative interpretation (see Tienari et al., 2004; Wahlberg et al., 1997). Some independent work reported by Kinney and colleagues (1997) also fails to show diminished mental health in adoptive parents raising children who later developed schizophrenia. Everything considered, the Finnish Adoptive Family Study has provided strong confirmation of the diathesis–stress model as it applies to the origins of schizophrenia.

MOLECULAR GENETICS Family studies tell us that schizophrenia runs in families, and twin and adoption studies help us explore the relative contributions of genes

and environment. These approaches also inform us about the genetic heterogeneity of schizophrenia. For example, in addition to higher rates of schizophrenia, higher rates of schizotypal personality disorder are also found in the relatives of patients with schizophrenia. This supports the idea of the schizophrenia spectrum and suggests that a genetic liability to schizophrenia sometimes manifests itself in a form of pathology that is "schizophrenia-like" but not exactly schizophrenia itself (see Lenzenweger, 2010).

The question now is not whether genes contribute to schizophrenia but which ones are involved. Researchers no longer believe that schizophrenia will, like Huntington's disease (see Chapter 14), be explained by one mutated gene on one specific chromosome. Current thinking is that, in most cases, schizophrenia probably involves many genes (many hundreds or more) working together to confer susceptibility to the illness. The individual's "dose" of schizophrenia genes may explain why one person develops schizophrenia and another develops a milder variant within the schizophrenia spectrum, such as schizotypal personality disorder.

Candidate genes are genes that are involved in processes that are believed to be aberrant in schizophrenia. An example is the *COMT* (catechol-O-methyltransferase) gene. This gene is located on chromosome 22 and is involved in dopamine metabolism. As you will soon learn, dopamine is a neurotransmitter that has long been implicated in psychosis (impaired reality testing). Interestingly, children who have a genetic syndrome (called *velocardiofacial syndrome*) that involves a deletion of genetic material on chromosome 22 are at high risk for developing schizophrenia as they move through adolescence (Gothelf et al., 2007). Prior to the onset of any disorder, they often report transient psychotic symptoms (such as auditory hallucinations) and have poor social functioning and reduced IQ (Debbané et al., 2006). Furthermore, as we shall see later, people with a particular variant of the *COMT* gene are much more likely to become psychotic as adults if they use cannabis during adolescence. For obvious reasons, schizophrenia researchers have been very interested in chromosome 22 and in the *COMT* gene in their search to understand the origins of the disorder. Other genes that have been implicated in schizophrenia are the *neuregulin 1* gene (located on chromosome 8), the *dysbindin* gene (on chromosome 6), the *DISC1* (which stands for "disrupted in schizophrenia") gene on chromosome 1, as well as several dopamine receptor genes (Gejman et al., 2011; Pogue-Geile & Yokley, 2010). Again, these candidate genes are involved in various neurobiological processes that are thought to have gone awry in schizophrenia.

One problem with candidate gene studies is that the findings from one study often fail to replicate in another study. But the field of molecular genetics is developing rapidly. One of the most important new tools for understanding the genetics of schizophrenia and other disorders involves the **genome-wide association study (GWAS)**. Unlike other genetic approaches where only a few genetic regions are tested, in a GWAS the entire genome is investigated. Typically two groups of participants are tested: one group that has the disease or disorder of interest (for example, schizophrenia) and another group that does not (the control or comparison group). Study participants provide a sample of DNA and then millions of genetic variants are explored and compared across the two groups. By using such an approach, researchers can identify single nucleotide polymorphisms (SNPs—pronounced "snips"), which are sequences of DNA, or other types of genetic variants, that are more frequently found in people with the disorder than without it. Of course, there is a difference between finding a genetic locus and finding the gene itself. But a good rule of thumb is that the relevant gene maybe the one closest to the locus that has been identified. One advantage of the GWAS method, therefore, is that this approach may help us detect genes that have very small effects but that might contribute to susceptibility for schizophrenia.

People with a particular variant of the COMT gene are much more likely to become psychotic as adults if they use cannabis during adolescence.

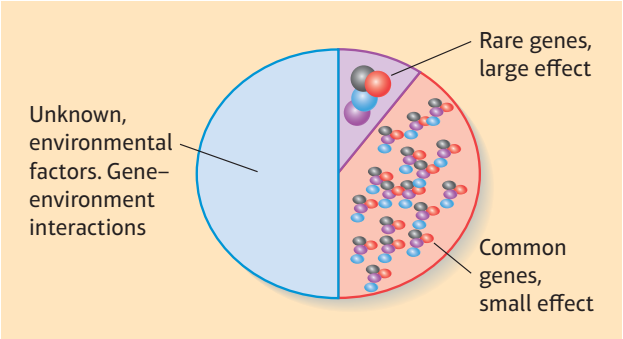
So what are the most recent findings? A groundbreaking new study has recently been published (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). This combines all GWAS data from all available schizophrenia samples into one single analysis of more than 150,000 people. The study has identified 108 loci that are associated with the presence of schizophrenia, 83 of which are newly discovered genetic regions. No one believes that this number of genetic loci will be sufficient to fully explain the genetics of schizophrenia (Flint & Munafò, 2014). Nonetheless, the findings have several important implications. First, they provide further evidence that a large number of alleles (an allele is an alternative form of a gene) are involved in creating genetic susceptibility for schizophrenia. Second, many of the genes that are implicated are involved in processes that have long been thought to be important for understanding schizophrenia. For example, some dopamine-related genes (such as *DRD2*) discriminated between people who had schizophrenia and people who did not. Other genetic regions that were identified in the analysis involved glutamate, another neurotransmitter

that, as we shall see soon, has been implicated in schizophrenia. Perhaps the biggest surprise, however, was that the strongest finding to emerge concerned a region on chromosome 6 that contains genes involved in immune functioning. The idea that schizophrenia could have something to do with immune function is a major new development. It is also, as you will soon learn, not as far fetched as it might appear at first glance.

Looking beyond schizophrenia itself, GWAS approaches are also telling us that some of the risk alleles that are being implicated in schizophrenia are implicated in bipolar disorder (Smoller, 2013). What this means is that, far from being distinct disorders (which is the impression one gets from reading the *DSM*), schizophrenia and bipolar disorder (at least at the genetic level) have a lot of overlap. Third, even though lots of common alleles likely work in combination to increase a person's risk for schizophrenia, rare alleles also probably play an important role (see Figure 13.4). Moreover, unlike the common alleles, these rare alleles are likely to be more specific to schizophrenia and not associated with increased risk for bipolar disorder. These rare alleles may result from mutations that compromise brain functioning in a negative way. Recent research has shown links between deletions and duplications of DNA (these are called *copy number variations* or CNVs) and schizophrenia. CNVs have also been implicated in autism, attention-deficit/hyperactivity disorder (ADHD), and intellectual disability (see Doherty et al., 2012). All of these conditions are characterized by mental challenges in various ways. Viewed in this way, schizophrenia may be one form of neurodevelopmental disorder with genetic links to autism, ADHD, and intellectual disability. Although much more remains to be learned, it is fast becoming clear that we can no longer consider schizophrenia to be a discrete disorder that (at least from a genetic perspective) is in a category of its own.

Figure 13.4 The multifactorial etiology of schizophrenia includes (1) rare genes that have a large effect, (2) common genes that have a small effect, and (3) the environmental factors and gene–environmental interactions that confer risk for schizophrenia.

(Adapted from Haller, C. S., Padmanabhan, J. L., Lizano, P., Torous, J., & Keshavan, M. (2014). Recent advances in understanding schizophrenia. *F1000Prime Reports 2014*, 6:57 (doi:10.12703/P6-57).)



ENDOPHENOTYPES We are certain that schizophrenia has a genetic basis. But progress has been frustratingly slow because schizophrenia appears to be very complex genetically. Another impediment is that researchers are still not sure exactly what phenotype (i.e., measurable characteristic of interest) they should be looking for (remember Bleuler's idea of "the schizophrenias"?). Because genetic analysis requires that we know who is "affected" and who is not, this is a big problem.

One solution is to focus on less complex and more homogenous phenotypes (such as specific symptom clusters) that may potentially be under the control of a smaller number of genes. Researchers are also exploring **endophenotypes**—discrete, stable, and measurable traits that are thought to be under genetic control. By studying different endophenotypes, researchers hope to get closer to specific genes that might be important in schizophrenia (Gottesman & Gould, 2003; Lenzenweger, 2010). Accordingly, researchers are interested in people who score high on certain tests or measures that are thought to reflect a predisposition to schizophrenia. One example is subjects who score high on a self-report measure of schizotypic traits involving perceptual aberrations and magical ideation (the Per-Mag Scale; see Chapman et al., 1982, 1994). Examples of items from these scales are shown in Table 13.1. Other endophenotypic risk markers for schizophrenia include abnormal performance on measures of cognitive functioning such as tests of working memory (see Barch, 2005; Lenzenweger, 2010). By studying these traits rather than the disorder itself, researchers hope to speed up progress in the search for the genes related to schizophrenia. Moreover, because many endophenotypes are not specific to schizophrenia (anhedonia is also characteristic of depression, for example) studying such traits may shed light on basic processes that have gone wrong in other disorders as well.

Table 13.1 Sample Items Measuring Psychosis-Proneness

Magical Ideation		
T	F	Things seem to be in different places when I get home, even though no one has been there.
T	F	I have sometimes felt that strangers were reading my mind.
T	F	At times, I have felt that a professor's lecture was meant especially for me.
Perceptual Aberration		
T	F	Sometimes people whom I know well begin to look like strangers.
T	F	Ordinary colors sometimes seem much too bright for me.
T	F	Now and then, when I look in the mirror, my face seems quite different than usual.

SOURCES: Chapman et al. (1978); Eckblad & Chapman (1983). Answering "true" to these items is more indicative of psychosis-proneness.

Prenatal Exposures

Whether or not a genotype is expressed depends on biological and environmental triggers. We now know that a range of environmental factors, including such things as maternal exposure to stress, are capable of influencing patterns of gene expression in the developing offspring. In the sections below we highlight some environmental risk factors that might either cause schizophrenia or trigger it in a genetically vulnerable person.

VIRAL INFECTION You have just learned that new genetic research is linking schizophrenia to the presence of genes involved with immune function. Although we are still are far from understanding what this might mean, the idea that schizophrenia might result from some kind of virus is not new. A century ago, Kraepelin (1919) suggested that "infections in the years of development might have a causal significance" for schizophrenia. We also know that in the Northern Hemisphere, more people with schizophrenia are born between January and March than would be expected by chance (Waddington et al., 1999). Could some seasonal factor, such as a virus, be implicated?

In 1957 there was a major epidemic of influenza in Finland. Studying the residents of Helsinki, Mednick and colleagues (1988) found elevated rates of schizophrenia in children born to mothers who had been in their second trimester of pregnancy at the time of the influenza epidemic. This study was the first of its kind and it was followed by several replication attempts. Some of these supported the link between maternal influenza and subsequent schizophrenia in the grown offspring. Others did not. But one problem with the design of these studies was that the researchers had no way of knowing whether the mothers actually had influenza during their pregnancies.

The first study to definitely test the maternal influenza–schizophrenia link was not done until 2004. Brown and colleagues (2004) analyzed specimens of maternal serum (serum is the clear liquid that separates out from coagulated blood). These had been routinely collected throughout the pregnancies of women in California and stored in an archive. This meant that they could be tested later for the presence of antibodies to influenza. The researchers were thus able to establish definitely which mothers had had influenza during their pregnancies. The results showed that influenza exposure during the first trimester of pregnancy was associated with a sevenfold increased risk of schizophrenia or schizophrenia spectrum disorders in the offspring. More generally, influenza exposure during the first half of pregnancy was associated with a threefold increase in risk. Because of the small sample size, neither of these results was statistically significant, although they were close ($P = 0.08$ and $P = 0.052$, respectively).

Although the size of the effect is small and influenza clearly does not account for very many cases of schizophrenia, the fact that any associations exist at all is very provocative. Other maternal infections such as rubella (German measles) and toxoplasmosis (a very common parasitic infection) that occur during pregnancy have also been linked to increased risk for the later development of schizophrenia (Brown, 2011; Khandaker et al., 2013). But how can maternal influenza set the stage for schizophrenia in a child two or three decades later? One possibility is that the mother's antibodies to the virus cross the placenta and somehow disturb brain development in the fetus. Another possibility is that influenza causes an increase in the production of inflammatory cytokines (you read about these in Chapter 5) that cause neurodevelopmental damage. Influenza could also have a direct and damaging effect on the developing brain (Brown, Begg, et al., 2004). As you will see in the Developments in Thinking box, these and other findings are making researchers more and more excited about the possible causal role of infection and immunity in schizophrenia.

RHESUS INCOMPATIBILITY Another example of how the mother's immune system might damage the developing brain of the fetus comes from a completely different source. Rhesus (Rh) incompatibility occurs when an Rh-negative mother carries an Rh-positive fetus. (Rhesus-positive or -negative is a way of typing a person's blood.) Incompatibility between the mother and the fetus is a major cause of blood disease in newborns. Interestingly, Rh incompatibility also seems to be associated with increased risk for schizophrenia. Hollister, Laing, and Mednick (1996) have shown that the rate of schizophrenia is about 2.1 percent in males who are Rh-incompatible with their mothers. For males who have no such incompatibility with their mothers, the rate of schizophrenia is 0.8 percent—very near the expected base rate found in the general population. Hollister is another example of a schizophrenia researcher who has a family member with the disorder, in this case a sister who was Rh-incompatible with her mother.

How might Rh incompatibility increase the risk for schizophrenia? One possibility is that the mechanism involves oxygen deprivation, or hypoxia. This suggestion is supported by studies that have linked the risk for schizophrenia to birth complications. Recent research also suggests that incompatibility between the blood of the mother and the blood of the fetus may increase the risk of brain abnormalities of the type known to be associated with schizophrenia (Freedman et al., 2011).

PREGNANCY AND BIRTH COMPLICATIONS Patients with schizophrenia are much more likely to have been born following a pregnancy or delivery that was complicated in some way (Cannon et al., 2002). Although the type of obstetric complication varies, many delivery problems (e.g., breech delivery, prolonged labor, or the umbilical cord around the baby's neck) affect the oxygen supply of the newborn. Although we still have much to learn, the

Developments in Thinking

Could Schizophrenia Be an Immune Disorder?

Evidence is growing that prenatal exposure to maternal infections may increase the risk of schizophrenia in offspring years later. But how could this work? The mother's inflammatory response may be a key factor. In an important new study Canetta and colleagues (2014) measured levels of C-reactive protein in stored serum samples taken from mothers during the first and second trimesters of their pregnancies. C-reactive protein (which you first encountered in Chapter 5) is a well-established marker of inflammation. What Canetta and colleagues found was that when maternal levels of C-reactive protein were high, the offspring had a nearly 60 percent higher risk of developing schizophrenia decades later.

But why was C-reactive protein elevated at all? Infections in the mother are obvious candidates. High levels of stress also increase inflammation. Researchers believe that early exposure to inflammatory processes at critical times in development might have effects on brain development. So if high levels of maternal C-reactive protein lead to high levels of C-reactive protein in the brain of the developing offspring, bad things may result. In essence the brain may be primed to develop schizophrenia later in life, especially if another "hit" is encountered. This hit could take many forms and might include some of the risk factors (obstetric complications, head injury, migration) that we describe elsewhere in the chapter.

It also warrants mention that the most current genetic research on schizophrenia is implicating genes on chromosome 6 that are involved in immune function. At first this may seem strange. But these genes also play a role in brain development. Do these genes get turned on by inflammation and so change how the brain develops? Or do some forms of these genes make a person more vulnerable to other negative effects of inflammation? It is too soon to put all the pieces together. What is interesting though is that people with schizophrenia have a 53 percent increased risk of developing autoimmune diseases such as psoriasis, Crohn's disease, and multiple sclerosis (Benros et al., 2014). And people with autoimmune diseases are at increased risk of developing schizophrenia (Eaton et al., 2010). So there is now an established link between schizophrenia and autoimmune disorders.

Taken together, all of these findings suggest we might do well to start thinking about schizophrenia as a disorder that might arise from exposure to an inflammatory state in prenatal life or early after. They also raise the possibility that a genetic vulnerability to schizophrenia could take the form of a genetic vulnerability toward dysregulation of the immune system (Cannon et al., 2014). Finally, inflammatory models of schizophrenia suggest new and exciting avenues for prevention. If we can protect pregnant women from infections or from high levels of stress, might this eventually lead to a decrease in rates of schizophrenia?

research again points toward damage to the brain at a critical time of development.

EARLY NUTRITIONAL DEFICIENCY Yet another piece of evidence that supports the idea that schizophrenia might be caused or triggered by environmental events that interfere with normal brain development comes from a tragedy that occurred in the Netherlands toward the end of World War II. In October 1944, a Nazi blockade resulted in a severe famine that affected people living in Amsterdam and other cities in the west of the country. The Dutch Hunger Winter (as it was known) continued until the Netherlands was liberated in May 1945. The population was severely malnourished during this time, and many died of starvation. Not surprisingly, fertility levels fell and the birth rate dropped precipitously. However, some children were born during this time. Those who were conceived at the height of the famine had a twofold increase in their risk of later developing schizophrenia (Brown, 2011). Early prenatal nutritional deficiency appears to have been the cause. Whether the problem was general malnutrition or the lack of a specific nutrient such as folate or iron is not clear. But again, something seems to have compromised the development of the fetus during a critical stage.

MATERNAL STRESS If a mother experiences an extremely stressful event late in her first trimester of pregnancy or early in the second trimester, the risk of schizophrenia in her child is increased (King et al., 2010). For example, in a large population study conducted in Denmark, the death of a close relative during the first trimester was associated with a 67 percent increase in the risk of schizophrenia in the child (Khashan et al., 2008). Currently, it is thought that the increase in stress hormones that pass to the fetus via the placenta might have negative effects on the developing brain, although the mechanisms through which maternal stress increases risk for schizophrenia are not yet well understood.

Genes and Environment in Schizophrenia: A Synthesis

Without question, schizophrenia has a strong genetic component. Current thinking is that genetic risk for schizophrenia emerges in one of two ways. The first is from large numbers (perhaps even thousands) of common genes. The individual contribution of each of these genes is likely very small. However, when all of these genetic variants interact together, they set the stage for the development of the illness. The other way that schizophrenia may arise is because of very rare genetic mutations. These could be highly specific to certain people or to certain families (see Crow, 2007;

McClellan, Susser, & King, 2007). These genetic events might involve microdeletions (bits of the DNA sequence that are missing in some places) or problems in the DNA sequence itself (such as repetitions of specific sections; St. Clair, 2009).

It is also possible that the focus on MZ concordance rates has caused us to overestimate the heritability of schizophrenia. This is because some MZ, and all DZ, twins do not have equally similar prenatal environments. Around two-thirds of MZ embryos are monochorionic, which means they share a placenta and blood supply. The remaining MZ twins and all DZ twins are dichorionic; they have separate placentas and separate fetal circulations. This is shown in Figure 13.5. The higher concordance rate for schizophrenia in MZ than in DZ twins might therefore be a consequence, at least in part, of the greater potential for monochorionic MZ twins to share infections. Davis, Phelps, and Bracha (1995) have found that MZ twins who are monochorionic are much more likely to be concordant for schizophrenia (around 60 percent concordance) than MZ twins who are dichorionic (around 11 percent concordance). The concordance figure for dichorionic MZ twins is very similar to that generally reported for DZ twins. Monochorionic MZ twins may therefore have inflated concordance rates in schizophrenia, which may have caused us to overattribute to genetics what might more accurately be attributed to environmental influences.

Finally, we need to keep in mind that genes get "turned on" and "turned off" in response to environmental changes. MZ twins who are discordant for schizophrenia show differences in their gene expression (Petronis et al., 2003). Perhaps some environmental "hits" turn on the genes for schizophrenia in one twin and not in the other. And perhaps some environments can keep the genes for schizophrenia from ever being turned on at all. Unfortunately, consistent with the diathesis–stress perspective, being at genetic risk does seem to make people more susceptible to environmental insults. In a study looking at the consequences of birth complications, Cannon and colleagues (1993) found that only the people who had a parent with schizophrenia and who had birth complications later showed brain abnormalities in adulthood such as enlarged ventricles (fluid-filled spaces in the brain). Moreover, for people who had two parents with schizophrenia, the problems were even worse. In contrast, people with no family history of schizophrenia did not show enlarged ventricles regardless of whether they experienced delivery complications when they were born. The message seems to be clear: A genetic liability to schizophrenia may predispose an individual to suffer more damage from environmental insults than would be the case in the absence of the genetic predisposition.

A Neurodevelopmental Perspective

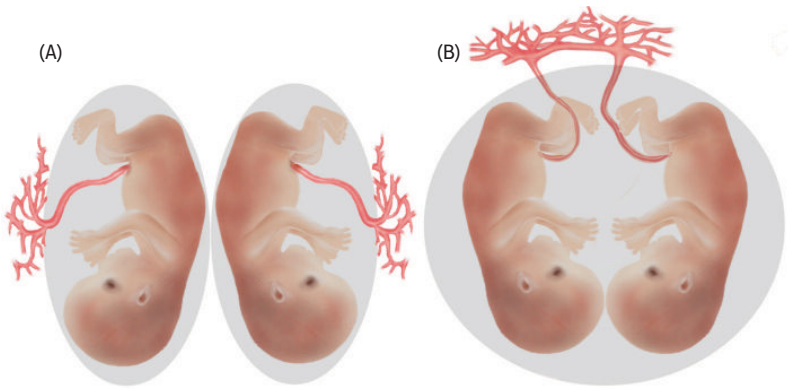
Earlier in this chapter you learned that schizophrenia typically strikes people in late adolescence or early adulthood. Yet in the sections above, we saw that some of the factors thought to cause schizophrenia occur very early in life—in some cases before birth. How can this be? Current thinking is that schizophrenia is a disorder in which the development of the brain is disturbed very early on. Risk for schizophrenia may start with the presence of certain genes that, if turned on, have the potential to disrupt the normal development of the nervous system. Exposure to environmental insults in the prenatal period may turn on these genes or may create problems in other ways, independently of genotype. What this means is that the stage for schizophrenia, in the form of abnormal brain development, may be set very early in life. Nonetheless, problems may not be apparent until other triggering events take place or until the normal maturation of the brain reveals them. This may not occur until the brain is fully mature, typically late in the second decade of life (Conklin & Iacono, 2002; Weinberger, 1987).

What goes wrong? We are not yet certain. Brain development is a complex process that involves a programmed, orderly, and progressive sequence of events (Romer & Walker, 2007). For example, if brain development were disrupted during important stages of cell migration, some cells might fail to reach their target destinations, greatly affecting the "internal connectivity" of the brain. (Organic solvents used in the dry cleaning business might disrupt fetal

Figure 13.5 Chorionic Arrangements in Twins

(A) Dichorionic twins, who can be either dizygotic or monozygotic, have separate placentas and separate fetal circulation. (B) Monochorionic twins, who are always monozygotic, have a single placenta and shared circulation.

(From Davis, J. O., Phelps, J. A., & Bracha, H. S. (1995). Prenatal development of monozygotic twins and concordance for schizophrenia. *Schizophrenia Bulletin*, 21(3), 357–366.)



neurodevelopment and so explain why having a parent who works as a dry cleaner triples the risk of schizophrenia in the offspring.) As we have already described, some of the genes that have been implicated in schizophrenia are known to play a role in brain development and neural connections. For example, earlier you learned that one region of the genome that has been linked to schizophrenia contains genes that are involved in immune functioning. This region (which is called the major histocompatibility complex (MHC) also plays an important role in brain development and neuronal function. Although very speculative at this time, it is possible genetic vulnerability to schizophrenia could be explained by greater genetic vulnerability to infection. It is also possible that infection could affect gene expression (which genes are turned on or off) and lead to changes in brain development that "prime" the brain for the later onset of schizophrenia. Although we still have much to learn about how all the facts fit together, problems in brain development and maternal inflammation or infection during pregnancy are very much implicated. In the next few years we expect some exciting new leads to emerge.

If the seeds of schizophrenia are sown so early in life, can we see early indications of vulnerability to the disorder before the illness itself strikes? An ingenious series of studies reported by Walker and colleagues nicely illustrates the association between early developmental deviation and schizophrenia risk. These investigators gathered family home movies made during the childhoods of 32 people who eventually developed schizophrenia. Trained observers made "blind" ratings (i.e., the observers were uninformed of outcomes) of certain dimensions of the emotional (Grimes & Walker, 1994) and facial expressions (Walker et al., 1993), motor skills, and neuromotor abnormalities (Walker et al., 1994) of these children and their healthy-outcome siblings from the same movie clips. The facial and emotional expressions and the motor competence of the "preschizophrenia" and the healthy-outcome children were found by the raters to differ significantly. The "preschizophrenia" children showed more motor abnormalities including unusual hand movements than their healthy siblings; they also showed less positive facial emotion and more negative facial emotion. In some instances these differences were apparent by age 2. Of course, we must keep in mind that these early problems do not characterize all children who will later develop schizophrenia. But they do tell us that subtle abnormalities can be found in children who are vulnerable to the disorder. We should also note that a major advantage of Walker's research design was that it avoided the problem of retrospective bias. Rather than asking parents or siblings what patients were like when they were growing up, the study used home movies to provide an objective behavioral record.

Another way to explore childhood indicators without the problem of retrospective bias is to use a prospective research design (see Chapter 1). Jones and colleagues (1994) and Isohanni and colleagues (2001) studied whole cohorts of children born in particular years and followed them up over time. Both groups of researchers found evidence of delayed speech and delayed motor development at age 2 in children who later went on to develop schizophrenia.

Yet another approach is to follow children who are known to be at high risk for schizophrenia by virtue of their having been born to a parent with the disorder. This strategy, pioneered decades ago by Mednick and Schulsinger (1968), has led to several other studies of high-risk children (for reviews, see Cornblatt et al., 1992; Erlenmeyer-Kimling & Cornblatt, 1992; Neale & Oltmanns, 1980; Watt et al., 1984). Obviously, research of this kind is both costly and time consuming. It also requires a great deal of patience on the part of researchers because children at risk have to be identified early in their lives and then followed into adulthood. Moreover, because the majority of people with schizophrenia do not have a parent with the disorder (in fact, 89 percent of patients have no first- or second-degree relatives with schizophrenia [Gottesman, 2001]), high-risk samples are not particularly representative. Nonetheless, they have provided us with some valuable information about what people at risk look like prior to developing the full illness.

Ratings of clips of old home movies revealed that children who went on to develop schizophrenia showed more unusual hand movements than their healthy siblings, even when they were just 2 years old.

One of the most consistent findings from high-risk research is that children with a genetic risk for schizophrenia are more deviant than control children on research tasks that measure attention (Erlenmeyer-Kimling & Cornblatt, 1992). Adolescents at risk for schizophrenia are also rated lower in social competence than adolescents at risk for affective illness (Dworkin et al., 1994; Hooley, 2010). Some of the social problems that these high-risk children have may result from underlying attentional problems (Cornblatt et al., 1992).

Echoing the findings from Walker's home movie study is evidence that early motor abnormalities might be an especially strong predictor of later schizophrenia. Using data from the New York High-Risk Study, Erlenmeyer-Kimling and colleagues (1998) reported that, of an initial group of 51 high-risk children, 10 developed schizophrenia or schizophrenia-like psychosis as adults. Of these, 80 percent had shown unusual motor behavior when they were between 7 and 12 years of age. In another study, adolescents at high risk for schizophrenia showed more movement abnormalities (e.g., facial tics, blinking, tongue thrusts) than either nonclinical controls or adolescents with personality or behavioral problems (Mittal et al., 2008). Moreover, these movement abnormalities became more marked with time and also became more strongly correlated with psychotic symptoms as the children got older. Although we might have suspected that schizophrenia would first begin to show itself via hallucinations or delusions, it may be that the first signs of the illness can instead be found in the way that children move. This could be because movement abnormalities and psychotic symptoms share some of the same neural circuitry in the brain. Problems in this neural circuitry might show themselves first via movement abnormalities. Then, as the brain matures, problems in the same neural circuits manifest themselves in psychotic symptoms (see MacManus et al., 2011; Mittal et al., 2008).

The original high-risk studies have given us many insights into the problems that characterize people at risk for schizophrenia. But researchers have now changed their strategies. A new generation of high-risk studies is focusing on young people who are at clinical (as opposed to genetic) high risk. By focusing on those who are already showing some **prodromal**, or very early, signs of schizophrenia, researchers are hoping to improve their ability to detect, and also perhaps intervene with, people who appear to be on a pathway to developing the disorder (Addington et al., 2007; Cannon et al., 2007). Recognizing this, the new diagnosis of **attenuated psychosis syndrome** (see Fusar-Poli et al., 2014) has entered *DSM-5* as a disorder in need of further study. More information about this condition is provided in the Thinking Critically about *DSM-5* box.

What kinds of problems do people with attenuated psychotic symptoms have? One of the most frequently reported difficulties involves being perplexed by reality

DSM-5 Thinking Critically about *DSM-5*

Attenuated Psychosis Syndrome

There was lively debate about whether a new diagnosis called attenuated psychosis syndrome should be added to the *DSM-5* (Carpenter & Van Os, 2011). In the end it was decided that the syndrome should be included in a provisional manner and placed in a section reserved for disorders in need of further study. But what is attenuated psychosis syndrome and why is it such a controversial diagnosis?

Attenuated psychosis syndrome is characterized by mild psychotic symptoms that are not severe enough to meet clinical criteria for another full-blown psychotic disorder. People with this syndrome are thought to be at risk for later psychosis. They are also experiencing some distress or disability and are seeking help for their problems. Proponents of including the syndrome in *DSM-5* argued that it would help clinicians identify these people and provide them with treatment at an early stage. This could, in theory, reduce distress in the short term and prevent the onset of a full-blown psychotic disorder in the long term. This is important because, once schizophrenia has developed, most patients are likely to experience recurring positive and negative symptoms, as well as persistent impairments in their work or social functioning for a large part of their lives (Jobe & Harrow, 2010).

Although these may seem like valid reasons to include the new diagnosis, there are also arguments against doing so. The potential for stigma is one problem (Yang et al., 2013). Another concern is that the majority of people who are identified as being at high risk are not on their way to developing a psychotic disorder. Addington and colleagues (2011) followed 303 young adults who were showing prodromal symptoms of schizophrenia. At the end of the follow-up period the majority of these young people (71 percent) had not made the transition into psychosis. Although the follow-up period was relatively short it seems that the false-positive rate here is very high (see also Fusar-Poli et al., 2012).

Another concern is that the existence of the diagnosis will increase the likelihood that antipsychotic medications will be used to treat it (see Weiser, 2011). But is it really appropriate and ethical to prescribe antipsychotic medications to someone who has only mild psychotic symptoms? Second-generation antipsychotic medications are not as effective as had been initially hoped. They also appear to be associated with some very undesirable changes (such as tissue loss) in the brain (Ho et al., 2011; Lewis, 2011). When used long term, they may even perpetuate psychosis (see the Unresolved Issues feature at the end of this chapter). Given this, it behooves us to be cautious with their use.

The inclusion of attenuated psychosis in Section III of the *DSM* may be a good interim solution. It will encourage more research into this new disorder. This may help us refine and improve the diagnostic criteria that are currently being used. More research may also stimulate the development of new treatment approaches capable of providing clinical benefits to patients without exposing them to unnecessary risks.

(e.g., confusing dreams with reality). People also reported losing control over the content of their thoughts or having ideas of being regarded in a negative way by others. Suspiciousness of friends or acquaintances was also characteristic, as was hearing sounds such as buzzing, hissing, knocking, or footsteps (Marshall et al., 2014). Note that these are all below the level of full-blown psychotic symptoms with regard to their severity. However, the presence of such experiences suggests that someone could be at risk of developing psychosis at a later point.

in review

- What evidence supports a genetic contribution to schizophrenia?
- Describe five environmental factors that have been shown to increase risk for schizophrenia.

Structural and Functional Brain Abnormalities

13.5 Discuss how the brain is affected in schizophrenia.

Technological developments now allow us to study the brain in ways that used to be impossible. These new approaches are revealing abnormalities in the structure and function of the brain as well as in neurotransmitter activity in people with schizophrenia. In the sections that follow we describe some of the problems in cognitive functioning that have long been known to characterize people with this disorder. We then consider what abnormalities in the structure and functioning of the brain might be responsible for these and other problems.

Neurocognition

Cognitive impairment is regarded as a core feature of schizophrenia. People with schizophrenia perform much worse (on average almost a full standard deviation worse) than healthy controls on a broad range of neuropsychological tests (see Heinrichs, 2005; Heinrichs & Zakanis, 1998). Almost all aspects of cognition (involving attention, language, and memory) are impaired. Nonetheless, we should keep in mind that not all patients show impairments in all areas and some perform within the normal range of functioning. However, even these patients may be showing significant declines from their earlier levels of cognitive functioning (Keefe, 2014).

Cognitive impairments appear early. Even before they have a diagnosable illness, young people at clinical high risk for developing psychosis perform less well than healthy controls on certain neurocognitive tests (Corigliana et al., 2014). Because cognitive difficulties can be seen right from the start of the illness (or even well before), it is unlikely that they are due to the effects of extended hospitalizations or medications. Indeed, very recent research suggests that having a lower IQ may itself be an independent risk factor for developing schizophrenia at a later point and that having a higher IQ may be protective in some way (Kendler et al., 2015).

Although people with lower IQs may (for reasons we do not yet understand) be more susceptible to developing schizophrenia, it is nonetheless the case that any preexisting cognitive impairments become more prominent and extensive as the illness progresses. What this means is that the cognitive impairments we see in patients experiencing their first episodes of illness are more severe and more wide ranging than the cognitive impairments found in people in the early (premorbid or prodromal) phases. It is also noteworthy that patients who have only recently become ill perform about the same on neuropsychological tests as patients who have been ill for many years (McCleery et al., 2014; Mesholam-Gately et al., 2009). For this reason researchers think that a sharp decline in cognitive ability (and IQ) occurs during the period of transition from the premorbid period into full-blown illness (Meier et al., 2014). After the first psychotic episode, the cognitive decline seems to stabilize (Nuechterlein et al., 2014). However, there may be a second period of deterioration that begins around age 65 (Harvey, 2014).

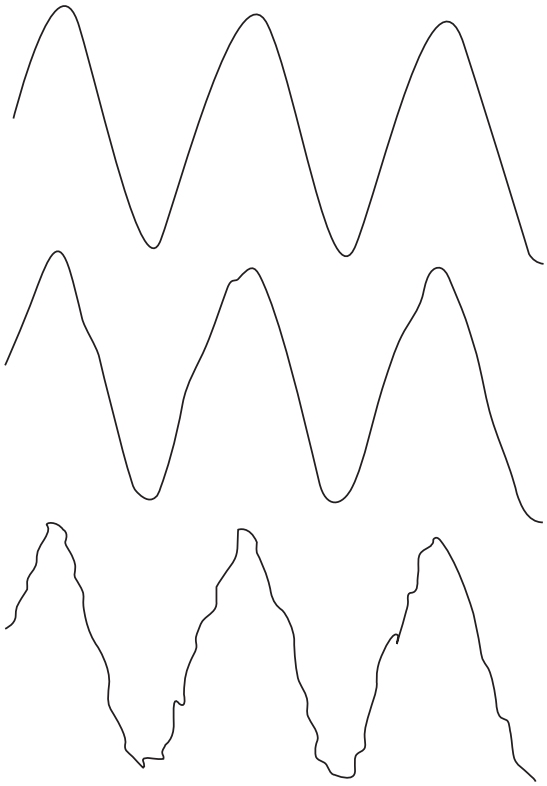
What kind of cognitive problems do people with schizophrenia show? Many examples can be given. For example, when asked to respond to a stimulus as quickly and appropriately as possible (this is a measure of reaction time), patients with schizophrenia do poorly compared with controls (see Nuechterlein, 1977). In addition, they show deficits on the Continuous Performance Test (CPT; e.g., Cornblatt et al., 1989). This task requires the subject to attend to a series of letters or numbers and then to detect an intermittently presented target stimulus that appears on the screen along with the letters or numbers (e.g., "Press when you see the number 7"). There are also problems with working memory (Barch, 2005; Park et al., 1995), which can be thought of as our "mental blackboard." When they engage in tasks of working memory, patients with schizophrenia show less prefrontal brain activity compared to healthy controls (Cannon et al., 2005).

Deficits are even apparent in the very earliest stages of visual and auditory processing. For example, somewhere between 54 and 86 percent of people with schizophrenia show eye-tracking dysfunction (see Figure 13.6) and are deficient in their ability to track a moving target such as a pendulum (Cornblatt et al., 2008). This is a skill referred to as smooth-pursuit eye movement (Levy et al., 2010). In contrast, only about 6 to 8 percent of the general population shows problems with eye tracking. Especially interesting is that around 50 percent of the first-degree relatives of patients with schizophrenia also show eye-tracking problems even though they do not have schizophrenia

Figure 13.6 Normal and Abnormal Eye Tracking of a Sinusoidal Wave

The top pattern is the target, the middle pattern is a record of normal tracking, and the lowest pattern is the kind of abnormal record produced by some patients with schizophrenia.

(Figure from Levy et al. (1993). Eye tracking dysfunction and schizophrenia: A critical perspective. *Schizophrenia Bulletin*, *19*(3), 461–536. Used with permission of Oxford University Press.)



themselves (e.g., Iacono et al., 1992; Sporn et al., 2005). This suggests that disturbances in eye tracking have a genetic basis and that eye tracking may represent a viable endophenotype for genetic studies.

In the area of auditory information processing, people with schizophrenia show problems with a process called sensory gating (Heinrichs, 2001; Potter et al., 2006). When two clicks are heard in close succession, the brain (receiving the auditory signal) produces a positive electrical response to each click. This response is called P50 because it occurs 50 milliseconds after the click. In normal subjects, the response to the second click is less marked than the response to the first click because the normal brain dampens, or "gates," responses to repeated sensory events. If this didn't happen, habituation to a stimulus would never occur. Many patients with schizophrenia, in contrast, respond almost as strongly to the second click as to the first. This is referred to as "poor P50 suppression." First-degree family members of patients with schizophrenia are also more likely than controls to have problems with P50 suppression (Clementz et al., 1998).

Taken together, the weight of the evidence suggests that patients with schizophrenia have problems with both basic and higher-level cognitive processing. This makes the world very difficult for them. The following comment, from a patient with schizophrenia, illustrates the struggle in a personal way:

> *I have trouble concentrating and keeping my mind on one thing at a time, especially when I'm with people. I can hear what they're saying, but I can't keep up with them and make sense of the conversation. I lose my grip on being part of the conversation and drift off. It's not so bad when I'm talking with just one other person, but if I'm trying to tune in to a conversation with several people, things come in too fast and I get lost. It's hard for me to contribute to a conversation when the ideas get blurred. (Liberman, 1982, p. 78)*

Social Cognition

If you were having dinner and your partner stared at your dessert and commented on how delicious it looked, what conclusion would you draw? You would likely assume that your partner wanted a bite of your dessert. Social cognition is concerned with how we recognize, think about, and respond to social information including the emotions and intentions of others. In addition to having problems with basic neurocognitive processes, people with schizophrenia show significant impairments in social cognition (Pinkham, 2014). For example, they fail to spot the kinds of subtle (or not so subtle) social hints that most of us (as in the example about the dessert) can detect without difficulty. They also have difficulties recognizing emotion in faces (Kohler et al., 2010) and emotion being conveyed in speech (Hooker & Park, 2002). Compared to healthy controls, they are also less able to recognize when someone has made a social error (a faux pas) such as forgetting that a party is supposed to be a surprise. Social cognition seems to be especially compromised for people with schizophrenia. Patients with bipolar disorder, for example, when they are not in an episode of illness, perform as well as controls on such tests (Lee et al., 2013).

Of course, intact cognitive functions are required for a person to perform well on tests of social cognition. Nonetheless, although social cognition and nonsocial (neurocognition) are related, they are largely distinct constructs (Lee et al., 2013). Both help explain how well patients are able to function in the real world. However, when it comes to predicting social skills or quality of life, social cognitive abilities (such as social perception, emotion recognition, ability to detect irony and the like) seem to play a greater role than

neurocognitive skills such as attention or memory (Maat et al., 2012; Pinkham, 2014).

Loss of Brain Volume

Given the many impairments that are characteristic of schizophrenia, it is hardly surprising that we see brain abnormalities associated with the illness, both in terms of brain structure (what the brain looks like) and brain function (how the brain works). One of the most well-replicated findings concerns the brain ventricles. These are fluid-filled spaces that lie deep within the brain. Compared with controls, patients with schizophrenia have enlarged brain ventricles, with males possibly being more affected than females (Haijma et al., 2013; Lawrie & Abukmeil, 1998; Shenton et al., 2001). However, enlarged brain ventricles are not seen in all patients and are not specific to schizophrenia. They are also characteristic of patients with Alzheimer's disease, Huntington's disease, and chronic alcohol problems.

Enlarged brain ventricles are important because they are an indicator of a reduction in the amount of brain tissue. The brain normally occupies fully the rigid enclosure of the skull. Enlarged ventricles therefore imply that the brain areas that border the ventricles have somehow shrunk or decreased in volume, the ventricular space becoming larger as a result. In fact, MRI studies of patients with schizophrenia show about a 3 percent reduction in whole brain volume relative to that in controls (Hulshoff Pol & Kahn, 2008). This decrease in brain volume is present very early in the illness. Even patients with a recent onset of schizophrenia have lower overall brain volumes than controls (Steen et al., 2006; Vita et al., 2006) or else show evidence of enlarged ventricles (Cahn et al., 2002). These findings suggest that some brain abnormalities likely predate the illness rather than develop as a result of untreated psychosis or as a consequence of taking neuroleptic medications. Consistent with this, important new research shows that brain volume changes can be seen in genetically high-risk individuals as the illness is starting to develop. Indeed, it has been suggested that these changes may play a causal role in the onset of symptoms (Karlsgodt et al., 2010; Sun et al., 2009).

We also know that the brain changes that characterize people in the early stages of the illness progressively get worse with time. Cahn and colleagues (2002) measured changes in the overall volume of gray matter (which is made up of nerve cells) in patients who were experiencing their first episode of schizophrenia. Thirty-four patients and 36 matched, healthy comparison subjects received MRI brain scans at the start of the study and then again 1 year later. The results showed that the volume of gray matter declined significantly over time in the patients but not in the controls. More specifically, there was almost a 3 percent decrease in the volume of gray matter in the patients in the 1-year period between the first and the second scans. Figure 13.7 illustrates the progressive loss of gray matter over a 5-year period in another sample of adolescents with schizophrenia compared to healthy controls.

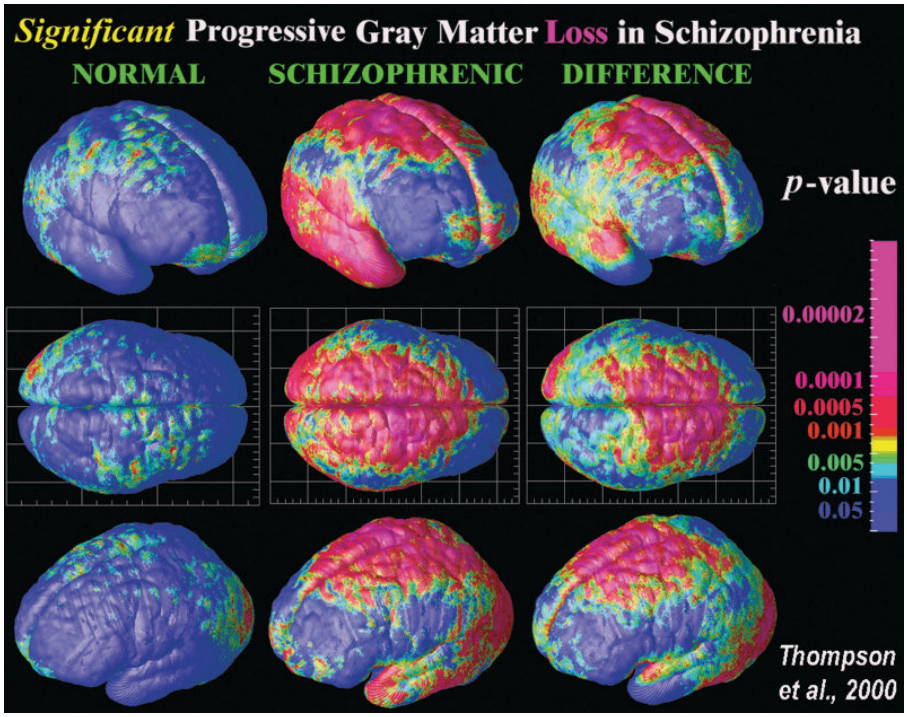
Studies of more chronically ill patients suggest that decreases in brain tissue and increases in the size of the brain ventricles are not limited to the early phases of this illness. Instead, progressive brain deterioration continues for many years. Moreover, these brain changes can also be found in MZ twins where one has schizophrenia and the other does not. The fact that brain changes are present in the discordant twin (the one without schizophrenia) suggests that they cannot be explained by the influence of antipsychotic medications and may instead be under genetic control (Brans et al., 2008; Hulshoff Pol & Kahn, 2008). Overall, the research findings suggest that in addition to being a neurodevelopmental disorder, schizophrenia is also a neuroprogressive disorder characterized by a loss of brain tissue over time. Kraepelin's use of the term *dementia praecox* may have been highly appropriate after all.

Affected Brain Areas

Are there regions of the brain that are especially implicated in schizophrenia? Although much remains to be learned, there is evidence of reductions in the volume of regions in the frontal and temporal lobes. These brain areas play critical roles in memory, decision making, and in the processing of auditory information. More specifically, there is a reduction in the volume of such medial temporal areas as the amygdala, which is involved in emotion; the hippocampus, which plays a key role in memory; and the thalamus, which is a relay center that receives almost all sensory input (Adriano et al., 2012; Haijma et al., 2013; Keshavan et al., 2008; Shenton et al., 2001). But reductions in gray matter are not invariably found. Recently, Ren and colleagues (2013) used MRI to compare the brains of 100 first-episode schizophrenia patients with 100 healthy controls who were comparable in terms of sex and years of education. This is the largest sample of patients studied so far. Unexpectedly, the patient group showed *increases* in gray matter volume in multiple brain areas. One thing that was different about the patients in this study was that they had not yet been treated with medications. In other words, they were all drug naïve. Although we still do not know how best to understand the findings from this study, the results challenge our thinking about brain changes associated with schizophrenia. Clearly, brain structure is abnormal in schizophrenia. But the nature of the abnormality (increased or decreased gray matter volume) may be linked to the stage of the illness, use of medications, or other factors that we still need to identify. As always, schizophrenia continues to be a disorder that does not give up its secrets easily.

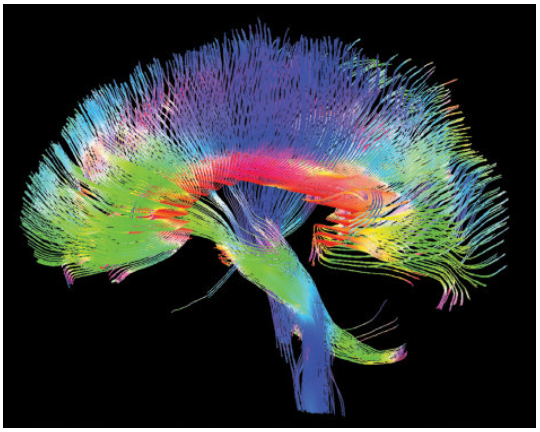
Figure 13.7 Progressive Gray Matter Loss in Schizophrenia

Compared with normal adolescents, young people with early-onset schizophrenia show a progressive loss of gray matter in their brains over time. MRI scans repeated over a 5-year period show a much greater loss of brain tissue in patients with schizophrenia than in healthy controls. Gray matter loss occurs in many brain areas, beginning in the parietal cortex and spreading to the temporal cortex and the frontal cortex.



White Matter Problems

When we talk about volume loss in the brains of people with schizophrenia we are referring to the loss of brain cells or gray matter. However, evidence is growing that schizophrenia also involves problems with white matter. Nerve fibers are covered in a myelin sheath (which looks white in color in a chemically preserved brain). Myelin acts as an insulator and increases the speed and efficiency of conduction between nerve cells. White matter is therefore crucially important for the connectivity of the brain. If there are disruptions in the integrity of white matter, there will be problems in how well the cells of the nervous system can function. For example, imagine the problems you would have in a group of networked computers if the connections that linked them were damaged in some way.

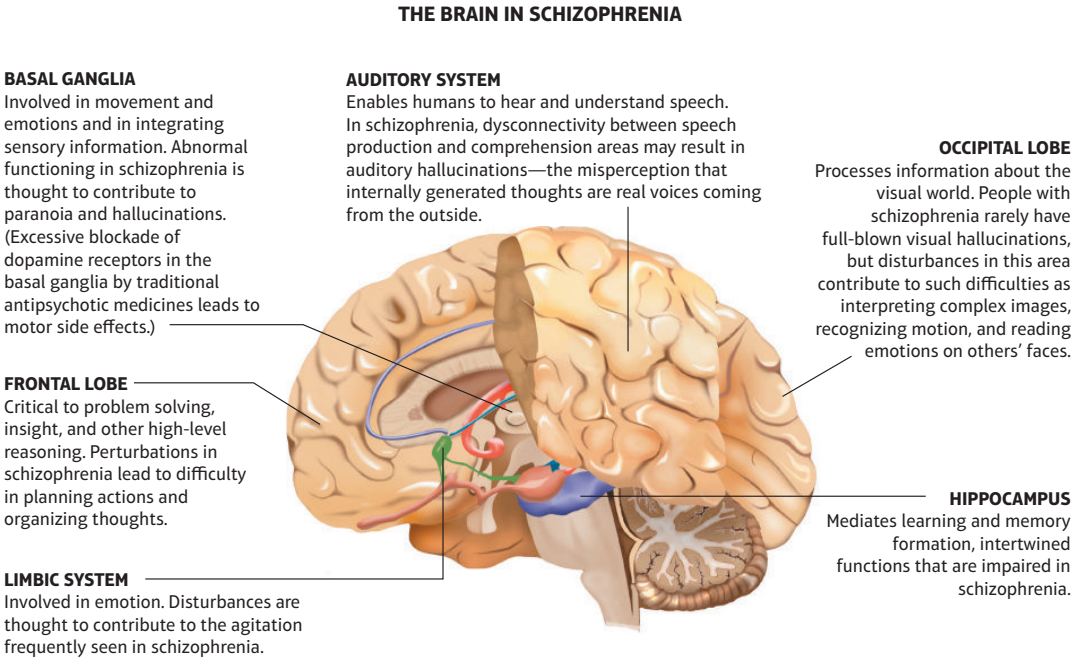


Nerve fibers are covered by a fatty myelin sheath, which looks white in a preserved brain (hence the term white matter). Myelin improves the electrical conductivity of nerve cells. This image illustrates white matter tracts (shown here in color for better clarity) and shows how interconnected the brain is.

Studies of patients with schizophrenia show that they have reductions in white matter volume as well as structural abnormalities in the white matter itself (Haijma et al., 2013). Interestingly, these abnormalities can be found in first-episode patients and also in people at genetic high risk for the disorder. This suggests that they are not a result of the disease itself or the effects of treatment. The fundamental problem seems to be one of dysconnectivity—abnormal integration between distinct brain regions, particularly those involving the frontal lobes (Pettersson-Yeo et al., 2011). This could help explain a lot about the clinical features of schizophrenia. For example, viewed in this way auditory hallucinations can be thought of as

Figure 13.8 The Brain in Schizophrenia

Many brain regions and systems operate abnormally in schizophrenia, including those highlighted here.



arising from a disconnection between language production and language comprehension areas. This could make internally generated speech (self-talk) seem as if it is being "heard."

At the clinical level, white matter abnormalities have been shown to be correlated with cognitive impairments (Kubicki et al., 2007). This makes sense if the connections that various brain regions have with the frontal lobes are not what they should be. In people at high risk of developing schizophrenia, white matter changes in the temporal areas of the brain also predict later social functioning (Karlsgodt et al., 2009). Another interesting recent finding is that children of people with schizophrenia, even though they are not psychotic themselves, have a reduction in the volume of the corpus callosum—a massive tract of white matter fibers that connects the two hemispheres of the brain (Francis et al., 2011). Although much remains to be learned, it is becoming increasingly clear that abnormalities in white matter, and in white matter development, may provide us with important additional insights into what goes wrong with the brain in schizophrenia.

Brain Functioning

Studies of brain functioning tell us what is going on in the working brain, either when it is engaged in a task or at rest. You have already learned about the structural brain abnormalities associated with schizophrenia and the problems that patients with schizophrenia have on various neurocognitive tests and on tests of social cognition. Given this, you will hardly be surprised to learn that neuroimaging research is showing us just how disrupted brain functioning is in patients with this disorder.

For example, some patients show abnormally low frontal lobe activation (known as "hypofrontality") when they are involved in mentally challenging tasks such as the Wisconsin Card Sorting Test (WCST) or in other tests generally thought to require substantial frontal lobe involvement. Essentially, this brain area does not seem to be able to kick into action when patients perform complex tasks (see Figure 13.8). In other patients, hyperactivation in frontal brain areas is found, suggesting that they are having to work harder to be successful on the task. In both sets of circumstances, however, the brain is not functioning in an optimal and efficient way.

Impaired functioning of the frontal lobes during cognitive tasks is also found in patients in the early stages of schizophrenia as well as in people at high risk for developing the disorder (Fusar-Poli et al., 2007). Again, however, it is important to remember that such alterations in functioning are not characteristic of all patients (e.g., Buchsbaum et al., 1992; Heinrichs, 2001). Nonetheless, frontal lobe dysfunction is believed to account for some of the negative symptoms of schizophrenia and perhaps to be involved in some attentional-cognitive deficits (Cannon et al., 1998; Goldman-Rakic & Selemon, 1997).

Dysfunction of the temporal lobe is also found, although here the findings are often not very consistent (Keshavan et al., 2008). However, what may be most important is that there may be a problem with the way activity in different brain regions gets *coordinated*. When we are at rest or relaxing and just involved in our own thoughts, there is activation in a network of brain regions that comprise the "default mode network." You can think of this as the brain on standby. Then, when we are actively engaged in a task, activity in this network of brain areas has to be suppressed in favor of activity in brain areas that are relevant to the task at hand. But imagine what might happen if it was difficult to disengage from the default mode. Performance on the task would suffer. This is what researchers now think may be happening in people with schizophrenia. Whereas healthy people find it easy to suppress activity in the default mode network (tuning their brains into the "correct station" so to speak), people with schizophrenia may not be able to do this as efficiently (Guerrero-Pedrazza et al., 2011; Ren et al., 2013; Whitfield-Gabrieli et al., 2009). This lack of ability to disengage the default mode network may help us understand why people with schizophrenia have so many difficulties with a wide range of tasks across a broad array of areas (Karlsgodt et al., 2010).

Cytoarchitecture

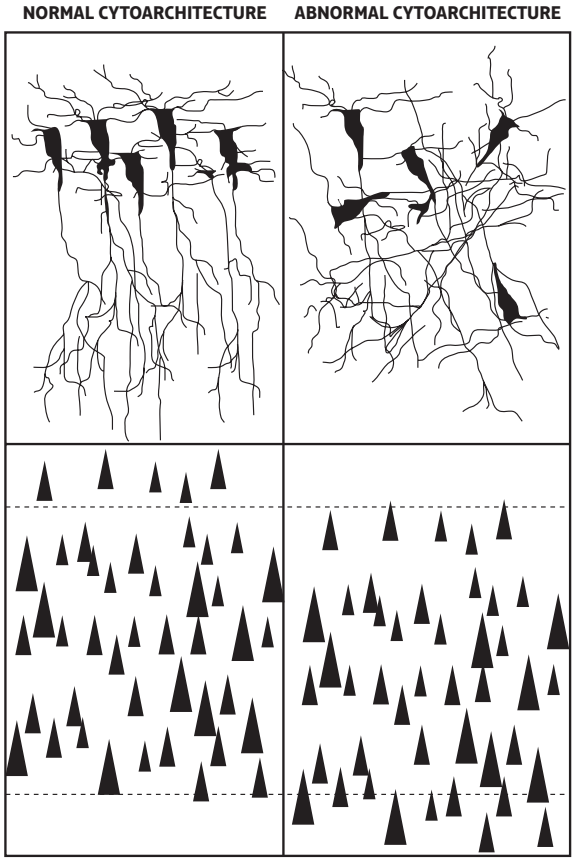
As we have seen, one hypothesis about schizophrenia is that genetic vulnerabilities, perhaps combined with prenatal insults, can lead to disruption of the migration of neurons in the brain. If this is true, some cells will fail to arrive at their final destinations, and the overall organization of cells in the brain (the brain's *cytoarchitecture*) will be compromised. This is illustrated in Figure 13.9.

The organization of cells in the brain appears to be disrupted in other ways as well. Using complex, three-dimensional counting techniques, researchers have reported an increase in neuronal density in some areas of the brains of patients with schizophrenia (see Selemon, 2004). There are also abnormalities in the distribution of cells in different layers of the cortex and hippocampus (Arnold, 2000; Kalus et al., 1997; Selemon et al., 1995). Of particular importance is the finding that patients with schizophrenia are missing particular types of neurons known as "inhibitory interneurons" (Benes & Berretta, 2001). These are called GABA interneurons and they are responsible for regulating the excitability of other neurons. (Essentially they tell other neurons to calm down.) Their absence may mean that bursts of activity by excitatory neurons in the brain go unchecked. Again, research suggests that the brains of patients with schizophrenia may be less able to regulate or dampen down overactivity in certain key neural circuits (see Daskalakis et al., 2002). As we will see shortly, patients with schizophrenia have difficulty handling even normal levels of stress. Given what we have just learned, this makes a great deal of sense.

Figure 13.9 Cytoarchitecture and Neural Development

The upper diagram shows examples of normal and abnormal pyramidal cell orientation in the hippocampus. The lower diagram is a schematic representation of stained neurons and the "downward-shift" phenomenon. Premature arrest of cell migration during development may underlie the high frequency of cells in lower regions close to white matter and their relative paucity near the cortical surface.

(Figure 7.1 from Heinrichs R. W. (2001). *In search of madness: Schizophrenia and neuroscience* (p. 196). Oxford University Press. Adapted from Arnold, S. E., & Trojanowski, J. Q. (1996). Recent advances in defining the neuropathology of schizophrenia. *Acta Neuropathologie, 92*, 217–31 and Kolb, B., & Wishaw, I. Q. (1996). *Fundamentals of human neuropsychology* (4th ed.). New York: Freeman.)



Did you ever wonder how research of this kind gets done? This is a topic that most of us do not think about (or perhaps care to think about) very much. But researchers owe a debt of gratitude to people who have generously donated their brains for scientific study after their death. In the United States and throughout the world, psychiatric brain banks provide brain tissue samples for use in schizophrenia research, as well as research on other psychiatric and neurodegenerative disorders including Alzheimer's disease (Deep-Soboslay et al., 2011). As you can imagine, there are many methodological issues associated with using postmortem

brain tissue to understand schizophrenia. These include the older age of the brains, the high level of comorbid substance abuse in patients, as well as medication effects. The scarcity of donations is also a challenge. For example, on average only 9 schizophrenia brains and 13 healthy control brains are donated to the tissue bank maintained by the National Institute of Mental Health (NIMH) each year.

Brain Development in Adolescence

Although we have every reason to believe that risk genes and early prenatal experiences compromise brain development in the fetus, the story may not end so early. The brain continues to develop and mature through adolescence and into young adulthood. For example, we all have an excess of synapses well into our late teens. However, normal processes that occur during adolescence prune (or reduce) these synapses, so decreasing "neuronal redundancy." There is also a normal reduction in gray matter volume that occurs in adolescence, as well as an increase both in white matter and in the volume of the hippocampus and the amygdala. In addition, the number of excitatory synapses decreases and the number of inhibitory synapses increases. All of these processes are thought to occur to enhance brain function overall and to make the brain more "adult" (Insel, 2010; Walker et al., 2010).

But what if these processes fail to occur in a normal way? Depending on what goes wrong and when, we might expect to see many of the differences (increased or reduced gray matter volume, less white matter, reduced volume of the hippocampus) that we do actually see in schizophrenia. In other words, we can think of schizophrenia as a disorder characterized by abnormal maturation (excessive pruning of synapses, abnormal myelination) of the brain and its networks.

Major brain changes take place during adolescence as the brain matures. If problems occur during this critical phase of development, schizophrenia may be the result.

The idea that schizophrenia involves abnormal or disrupted brain development is further supported by recent research linking schizophrenia to a history of head injury. People who have had a hospital contact for a head injury have a 65 percent increase in later risk for schizophrenia (Orlovska et al., 2014). This increased risk appears to be independent of having a family history of psychiatric illness. Furthermore, if the head injury occurs between the ages of 11 and 15, the risk of schizophrenia is increased even more (85 percent increase). All of this points to the possibility that there are sensitive periods in brain development when environmental insults might be especially damaging. Some of these probably occur very early in life, before or around the time of birth. Still others might occur much later. As we have said before, the etiology of schizophrenia is very complicated. But many of the answers undoubtedly lie in what goes wrong in the brain at critical periods of development.

Synthesis

The brain is compromised in schizophrenia, although the compromise is often very subtle. Some of the brain abnormalities that are found are likely to be genetic in origin. Others may reflect environmental insults. For example, Baaré and colleagues (2001) used MRI to study the brains of MZ and DZ twins who were discordant for schizophrenia and then compared the results for these groups to results from a group of healthy twins. What these researchers found was that the patients with schizophrenia had smaller brain volumes than their well co-twins. What was interesting, however, was that these well co-twins also had smaller brains than the healthy control twins. Baaré and colleagues propose that genetic risk for schizophrenia may be associated with reduced brain development early in life. This is why the healthy twins who had a co-twin with schizophrenia had smaller brain volumes than the healthy controls. Baaré and colleagues also hypothesize that patients who develop schizophrenia suffer additional brain abnormalities that are not genetic in origin. This explains why the twins with schizophrenia had smaller brain volumes than their discordant co-twins. In people at genetic risk for schizophrenia (but not in those without genetic risk), a history of fetal oxygen deprivation has been shown to be associated with brain abnormalities in later life (Cannon et al., 2002). In other words, what we may have here is an excellent example of how genes can create an enhanced susceptibility to potentially aversive environmental events. Moreover, even when both members of a twin pair have identical genes (as is the case for MZ twins), if only one of them experiences the environmental insult (for example, a birth cord around the neck, creating hypoxia or a perhaps a head injury), only one twin might be pushed across the threshold into illness while the co-twin remains healthy.

Finally, we emphasize that it is unlikely that schizophrenia is the result of any one problem in any one specific region of the brain. The brain is comprised of *functional circuits*—regions that are linked to other regions by a network of interconnections. If there is a problem at any point in the circuit, the circuit will not function properly. The focus now is on learning how the brain is wired and what regions are functionally linked. Research on the default mode network is an example of this. Subtle brain abnormalities in some key functional circuits (or deficiencies in the ability to switch from one functional circuit to another) may wreak havoc with normal functioning. As we gain more knowledge about how the brain does its job, we will understand more about how exactly the brain is compromised in schizophrenia.

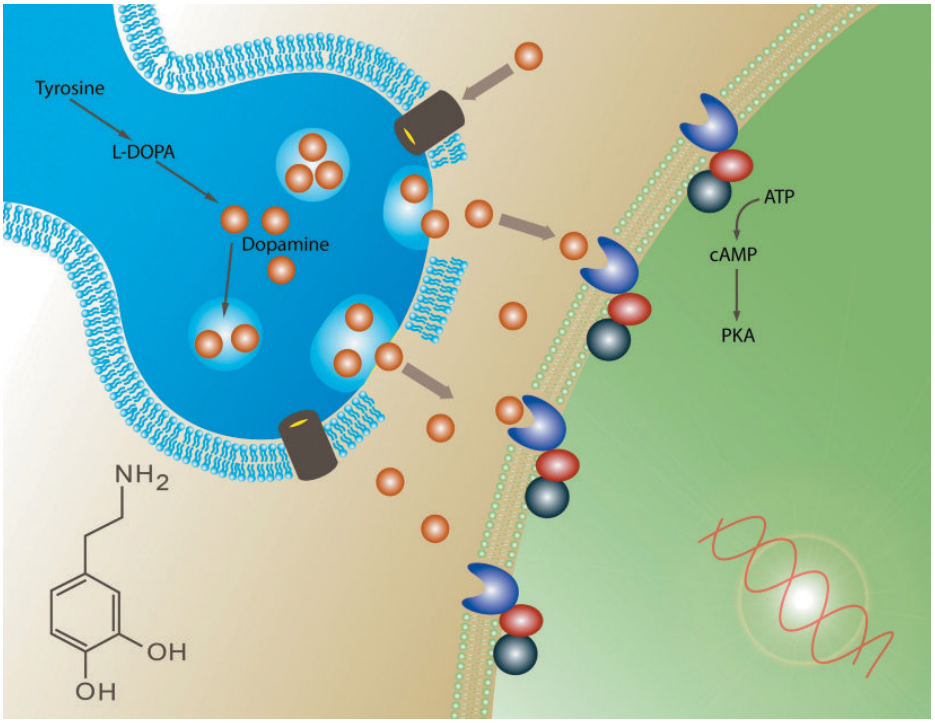
Neurochemistry

After researchers discovered in 1943 that LSD could cause profound mental changes, those interested in schizophrenia began to consider the possible biochemical basis of the disorder. Now the idea that serious mental disorders are due to "chemical imbalances" in the brain is commonplace. This phrase is often used to provide a general explanation of why someone has a disorder like schizophrenia. But the notion of "chemical imbalance" is vague and imprecise. All it really conveys is the widely accepted notion that alterations in brain chemistry may be associated with abnormal mental states.

The most well-studied neurotransmitter implicated in schizophrenia is **dopamine**. The *dopamine hypothesis* dates back to the 1960s and was derived from three important observations. The first was the pharmacological action of the drug chlorpromazine (Thorazine). Chlorpromazine was first used in the treatment of schizophrenia in 1952. It rapidly became clear that this drug was helpful to patients. Eventually, it was learned that the therapeutic benefits of chlorpromazine were linked to its ability to block dopamine receptors.

The second piece of evidence implicating dopamine in schizophrenia came from an entirely different direction. Amphetamines are drugs that produce a functional excess of dopamine (i.e., the brain acts as if there is too much dopamine in the system). In the late 1950s and early 1960s, researchers began to see that abuse of amphetamines led, in some cases, to a form of psychosis that involved paranoia and auditory hallucinations (Connell, 1958; Kalant, 1966; Tatetsu, 1964). There was thus clinical evidence that a drug that gave rise to a functional excess of dopamine also gave rise to a psychotic state that looked a lot like schizophrenia.

The third piece of indirect evidence linking dopamine to schizophrenia came from clinical studies that actually treated patients by giving them drugs that increase the availability of dopamine in the brain. An example here is



After being synthesized, dopamine is stored until it is released into the synapse. Dopamine binds to receptors on the postsynaptic neuron (shown in blue) triggering other reactions. It is then recycled back into the neuron to be used again.

Parkinson's disease, which is caused by low levels of dopamine in a specific brain area (the basal ganglia; see Figure 13.8) and is treated with a drug called L-DOPA. Psychotic symptoms are a significant complication of treatment with L-DOPA. Again, then, the circumstantial evidence pointed to the role of dopamine in inducing psychosis.

PET scans allow us to study the working brain and to look at dopamine synthesis as well as the density of dopamine receptors in living patients.

How could dopamine induce psychosis? Activity in the dopamine system may play a role in determining how much salience we give to internal and external stimuli. Dysregulated dopamine transmission may actually make us pay more attention to and give more significance to stimuli that are not especially relevant or important. This is called "aberrant salience" (see Kapur, 2003). If this is the case, it is quite easy to see why patients might develop delusions or experience hallucinations and why psychotic experiences might be so shaped by the patient's culture and history. In the early stages of their illnesses, patients often report heightened sensory awareness ("My senses were sharpened. I became fascinated by the little insignificant things around me") or increased meaning in events ("I felt that there was some overwhelming significance in this"). If dopamine creates aberrant salience, the person will struggle to make sense of everyday experiences that were previously in the background but that now have become inappropriately important and worthy of attention. In this way, the hum of a refrigerator could become a voice talking; or the arrival of a package could signal a threat, which then prompts the patient to look carefully at the subtle behaviors of others to see who could be a source of harm and persecution.

But how might a functional excess of dopamine in the system come about? One way is through too much dopamine being available in the synapse (the gap between nerve cells that has to be "bridged" by a neurotransmitter for a nerve impulse to be carried from one neuron to another). This could come about by increasing the synthesis or production of dopamine, by releasing more of it into the synapse, by slowing down the rate at which dopamine is metabolized or broken down once it is in the synapse, or by blocking neuronal reuptake (the "recycling" of dopamine back into the neuron). Any or all of these could increase the overall availability of dopamine. There are also ways in which a functional excess of dopamine could be produced or, more accurately, mimicked. If the receptors that dopamine acts on (i.e., those on the postsynaptic membrane) are especially dense and prolific or if they are especially sensitive (or both), the effects of a normal amount of dopamine being released into the synapse would be multiplied. In other words, the system acts as though there were more dopamine available even though there really isn't.

Before the development of highly sophisticated imaging techniques, researchers interested in learning about dopamine in the brains of people with schizophrenia could use one of two approaches. They could measure dopamine in the (postmortem) brains of deceased patients, or they could study dopamine indirectly by measuring its major metabolite (what most of it is converted into). The major metabolite of dopamine is homovanillic acid, or HVA. However, HVA is best collected in cerebrospinal fluid (CSF). This requires that the patient agree to a lumbar puncture, which involves a large needle being inserted into the spine to draw off fluid. Not only was this potentially dangerous, it also left the patient with a violent headache.

Research in this area has progressed rapidly in recent years thanks to technological developments, such as PET scans. These allow us to study the working brain and to look at dopamine synthesis as well as the density of dopamine receptors in living patients. There are five subtypes of dopamine receptors (D1–D5). Of these, the D2 receptor is the most relevant clinically, and most of the research has focused on this. So what do we know? The most current findings tell us that the biggest abnormality in dopamine functioning occurs presynaptically. In other words, too much dopamine (about 14 percent more) is being synthesized and released into the synapse (Fusar-Poli & Meyer-Lindberg, 2012; Howes et al., 2012). There is also some evidence that patients with schizophrenia have an increased number of D2 or D3 receptors. However, the difference is small and is not found in patients who have not taken antipsychotic medications. This suggests that elevations in dopamine receptor density are more likely linked to treatment effects rather than being integral to schizophrenia itself.

But dopamine is not the only neurotransmitter implicated in schizophrenia. Before leaving our discussion of neurochemistry, let's take a quick look at another key neurotransmitter that is attracting a lot of attention.

Glutamate is an excitatory neurotransmitter that is widespread in the brain. As was the case for dopamine, there are a number of reasons why researchers suspect that a dysfunction in glutamate transmission might be involved in schizophrenia. First, PCP, or angel dust, is known to block glutamate receptors. PCP also induces symptoms (both positive and negative) that are very similar to those of schizophrenia. Moreover, when people with schizophrenia take PCP, it exacerbates their symptoms.

Second, physicians had to stop using ketamine, which is an anesthetic, because when it is given intravenously to healthy volunteers, it produces schizophrenia-like positive and negative symptoms (see Krystal et al., 2005). When given to patients whose schizophrenia is stable and well controlled, ketamine exacerbates hallucinations, delusions, and thought disorder. But what is all the more remarkable about ketamine is that it does not cause any of these problems when it is administered to animals or to children, for whom it continues to be used as an anesthetic. This suggests that age (and brain maturity) determines whether ketamine causes psychosis.

Like PCP, ketamine blocks glutamate receptors. Researchers are now exploring concentrations of glutamate in the postmortem brains of patients with schizophrenia and finding lower levels of glutamate in both the prefrontal cortex and the hippocampus compared with the levels in control subjects (Goff & Coyle, 2001). Recent results from a meta-analysis further suggest that glutamate levels are also low in the brains of living patients who have schizophrenia (Marsman et al., 2011). This is exciting because, many years ago, Olney and Farber (1995) proposed that diminished activity at certain types of glutamate receptors (known as "NMDA" receptors) may not only trigger schizophrenia-like symptoms but may also cause the degeneration of neurons in key brain areas. In other words, if the NMDA receptors are not normally active (perhaps because glutamate levels are low), subtle brain damage may result.

For all of these reasons, the *glutamate hypothesis* of schizophrenia is now attracting a lot of research attention. It is also prompting the development of new experimental drugs that might provide additional ways to treat schizophrenia. For example, amino acids such as glycine and D-serine are now being used to enhance neurotransmission at NMDA receptor sites. This research is still in its early stages; nonetheless, the initial findings have promise (Javitt, 2012; Lane et al., 2008).

Finally, does the importance of glutamate challenge the importance of dopamine in the neurochemistry of schizophrenia? No. One action of dopamine receptors is to inhibit the release of glutamate. Simply stated, an overactive dopaminergic system could result in excessive suppression of glutamate, leading to the underactivity (hypofunction) of the NMDA receptors. The dopamine hypothesis of schizophrenia is actually made all the more credible by discoveries about glutamate.

in review

- Does schizophrenia involve problems with white matter? How do these patients perform on neurocognitive tests?
- How is the overall organization of cells in the brain of schizophrenics compromised?

Psychosocial and Cultural Factors

13.6 Explain the psychosocial and cultural factors associated with schizophrenia.

Biological factors play a key role in the development of schizophrenia. But, perhaps surprisingly, where and how people live is also of great importance.

Do Bad Families Cause Schizophrenia?

Years ago, parents were routinely assumed to have caused their children's disorders through hostility, deliberate rejection, or gross parental ineptitude. Many professionals blamed parents, and their feedback to them was often angry and insensitive. Mothers were particularly singled out for criticism. The idea of the "schizophrenogenic mother," whose cold and aloof behavior was the root cause of schizophrenia, was very influential in many clinical circles (Fromm-Reichman, 1948). This was very distressing for families. Not only were they faced with the difficulties of coping with a son or daughter who had a devastating illness, but they suffered all the more because of the blame that was directed toward them by mental health professionals.

Today, things are very different. Theories that were popular many decades ago—for example, the idea that schizophrenia was caused by destructive parental interactions (Lidz et al., 1965)—have foundered for lack of empirical support. Another idea that has not stood the test of time is the *double-bind hypothesis* (Bateson, 1959, 1960). A double bind occurs when the parent presents the child with ideas, feelings, and demands that are mutually incompatible (e.g., a mother may complain about her son's lack of affection but freeze up or punish him when he approaches her affectionately). According to Bateson's etiologic hypothesis, such a son is continually placed in situations where he cannot win, and he becomes increasingly anxious. Presumably, over time, such disorganized and contradictory communications in the family come to be reflected in his own thinking. However, no solid support for these ideas has ever been reported.

Instead, we have learned from past research that disturbances and conflict in families that include an individual with schizophrenia may well be caused by having a person with psychosis in the family (e.g., Hirsch & Leff, 1975). In other words, rather than causing the schizophrenia, family communication problems could be the result of trying to communicate with someone who is severely ill and disorganized (Liem, 1974; Mishler & Waxler, 1968). Of course, some families do show unusual communication patterns that we now refer to as "communication deviance" and which we described earlier. These amorphous and fragmented communications may actually reflect genetic susceptibility to schizophrenia on the part of the relative

(Hooley & Hiller, 2001; Miklowitz & Stackman, 1992). However, as we know from the Finnish Adoptive Family Study of Schizophrenia, adverse family environments and communication deviance probably have little pathological consequence if the child who is exposed has no genetic risk for schizophrenia (Tienari et al., 2004; Wahlberg et al., 1997).

Families and Relapse

Although schizophrenia is often a chronic disorder, its symptoms may be especially severe at some times (i.e., when there is a relapse) and less severe at other times (e.g., during a period of remission). Decades ago, George Brown and his colleagues (1958) observed that the kind of living situation patients with schizophrenia had after they left the hospital predicted how well they would fare clinically. Surprisingly, patients who returned home to live with parents or with a spouse were at higher risk of relapse than patients who left the hospital to live alone or with siblings. Brown reasoned that highly emotional family environments might be stressful to patients. He also suspected that what might be important was not the presence of markedly disturbed or pathological patient–family relationships (although those certainly existed in some families) but something much more ordinary and commonplace. Brown's hunch was that researchers should focus on "the range of feelings and emotions to be found in ordinary families" (see Brown, 1985, p. 22). This was an unusual insight at the time. But viewed today in the context of the diathesis–stress model, we see just how prescient Brown was.

In a series of studies, Brown and his colleagues went on to develop and refine the construct of **expressed emotion, or EE**. Expressed emotion is a measure of the family environment that is based on how a family member speaks about the patient during a private interview with a researcher (Hooley, 2007). It has three main elements: criticism, hostility, and emotional overinvolvement (EOI). The most important of these is criticism, which reflects dislike or disapproval of the patient. Hostility is a more extreme form of criticism that indicates a dislike or rejection of the patient as a person. Finally, EOI reflects a dramatic or overconcerned attitude on the part of the family member toward the patient's illness.

Expressed emotion is important because it has been repeatedly shown to predict relapse in patients with schizophrenia. In a meta-analysis of 27 studies, Butzlaff and Hooley (1998) demonstrated that living in a high-EE home environment more than doubled the baseline level of relapse risk for patients with schizophrenia in the 9 to 12 months after hospitalization. Moreover, even though EE predicts relapse regardless of whether the patients studied have been ill for a short, medium, or long time, EE seems to be an especially strong predictor of relapse for patients who are chronically ill.

Of course, it could be that families simply tend to be more critical of patients who are more severely ill. This would then explain why EE and relapse are correlated. However, the literature provides no strong support for this assumption (see Hooley et al., 1995). Also, EE predicts relapse even when potentially important patient variables are controlled statistically (Nuechterlein et al., 1992). Finally, research shows that when EE levels in families are lowered (usually by clinical interventions), patients' relapse rates also decrease (Falloon et al., 1985; Hogarty et al., 1986; Leff et al., 1982; McFarlane et al., 1995). This suggests that EE may play a causal role in the relapse process.

But how might EE trigger relapse? There is a great deal of evidence that patients with schizophrenia are highly sensitive to stress. Consistent with the diathesis–stress model, environmental stress is thought to interact with preexisting biological vulnerabilities to increase the probability of relapse (Nuechterlein et al., 1992). We know, for example, that independent stressful life events occur more frequently just prior to psychotic relapse than at other times (Ventura et al., 1989, 1992) and may exert their effects over longer periods of time too. Furthermore, one of the primary manifestations of the stress response in humans is the release of cortisol (a glucocorticoid) from the adrenal cortex. Animal and human studies show that cortisol release triggers dopamine activity (McMurray et al., 1991; Rothschild et al., 1985). Glucocorticoid secretion also affects glutamate release (Walker & Diforio, 1997). In other words, two of the major neurotransmitters implicated in schizophrenia (dopamine and glutamate) are affected by cortisol, which is released when we are stressed.

Along these lines, Hooley and Gotlib (2000) have suggested that, to the extent that high-EE behaviors exhibited by family members are perceived as stressful by patients, these behaviors are likely to trigger the release of cortisol. In support of this idea, high-EE relatives have been found to be more behaviorally controlling of patients than low-EE relatives are (Hooley & Campbell, 2002). When they try to help, they seem to do so in rather intrusive ways (e.g., "She wouldn't go to sleep so I held her head down onto the pillow"). Furthermore, controlling behaviors such as these predict relapse in patients with schizophrenia. Quite possibly, relatives' well-meaning attempts to get patients to function better simply backfire. If patients are stressed by what their relatives do, this could increase cortisol levels, affect important neurotransmitter systems, and perhaps eventually lead to a return of symptoms.

At the present time, we have no direct evidence that this happens. However, one study is worthy of note. A group of researchers studied the behavior of patients with schizophrenia when they were involved in interactions with high-EE and low-EE relatives (Rosenfarb et al., 1995). The researchers observed that when patients said something strange (e.g., "If that kid bites you, you'll get rabies"), high-EE relatives tended to respond by being critical of the patient. What was interesting was that when this happened,

it tended to be followed by another unusual remark from the patient. In other words, an increase in patients' unusual thinking occurred immediately after the patient was criticized by a family member. Although other interpretations of the findings are possible, the results of this study are consistent with the idea that negative (stress-inducing) behaviors by relatives can trigger increases in unusual thinking in patients with schizophrenia. Although we have no way of knowing what was happening to the cortisol levels of these patients, it is intriguing to speculate that increased cortisol release might somehow be involved.

Researchers are now using functional neuroimaging techniques (see Chapter 1) to learn more directly how EE affects the brain. Recent findings show that hearing criticism or being exposed to emotionally overinvolved comments leads to different patterns of brain activity in people who are vulnerable to psychopathology compared to healthy controls (Hooley et al., 2009; Hooley, Gruber, et al., 2010). We do not yet know if people who show this pattern of brain activation are at increased risk of relapse, although this might be expected.

Patients with schizophrenia who live in families where there is a high level of emotional tension have more than twice the risk of relapse.

Urban Living

Being raised in an urban environment seems to increase a person's risk of developing schizophrenia. Pederson and Mortensen (2001) studied a sample of 1.9 million people in Denmark, a country in which information about where people live is recorded in a national registry and people have to notify authorities when they change addresses in order to retain eligibility for benefits. The researchers found that children who had spent the first 15 years of their lives living in an urban environment were 2.75 times more likely to develop schizophrenia in adulthood than were children who had spent their childhoods in more rural settings. Other methodologically sound studies also confirm this association (Sundquist et al., 2004). It has been estimated that if this risk factor could be removed (that is, if we all lived in relatively rural settings) the number of cases of schizophrenia could decrease by about 30 percent (see Brown, 2011).

Immigration

The findings showing that urban living raises a person's risk for developing schizophrenia suggest that stress or social adversity might be important factors to consider with respect to this disorder. Supporting this idea, research is also showing that recent immigrants have much higher risks of developing schizophrenia than do people who are native to the country of immigration. Looking at the results of 40 different studies involving immigrant groups from many different parts of the world, Cantor-Graae and Selten (2005) found that first-generation immigrants (i.e., those born in another country) had 2.7 times the risk of developing schizophrenia; for second-generation immigrants (i.e., those with one or both parents having been born abroad), the relative risk was even higher at 4.5. In other words, there is something about moving to another country that appears to be a risk factor for developing schizophrenia. The following case study illustrates this.

Schizophrenia in an Immigrant from China

After she lost her job, Lian, a young Chinese woman, was sent by her parents to live in Ireland. Upon arrival, Lian lived first in a boarding house. She then moved into a house that she shared with eight other young Chinese. Lian enrolled in a language school and also began to study for a degree in business administration. She made very few friends and spent most of her time on her own reading or playing games. The people who knew her described her as being a very private person who usually preferred to be alone.

Lian's difficulties began after she learned that two young Chinese students in Dublin had died under suspicious circumstances. She became exceedingly alarmed—so much so that she left the language school and moved back into the boarding house to be with her former landlady. She began to believe that her abdomen contained a "presence" that was living there. She also reported hearing multiple voices coming from the "presence." These voices, which spoke both Chinese and English, included the voices of teachers from Lian's language school, her landlady, and her family from China. Lian reported that she had received a banknote from her family and that the picture on the banknote had spoken to her saying, "You are no longer welcome here." Lian also developed a delusion that the family who had raised her were not her real family. She rapidly cut off all contact with them and talked about wanting to find her "real mother." Lian also said that the CIA was searching for her. When questioned about why this should be the case, she was unable to say. (Based on Feeney et al., 2002.)

Why should immigration be associated with an elevated risk of developing schizophrenia? One possibility is that immigrants are more likely to receive this diagnosis because of cultural misunderstandings (Sashidharan, 1993). However, there is no convincing evidence that this is

the case (Harrison et al., 1999; Takei et al., 1998). Another hypothesis is that people who are genetically predisposed to develop schizophrenia are more likely to move to live in another country. However, some of the impairments associated with the early stages of schizophrenia seem incompatible with this idea because negative symptoms and frontal lobe dysfunctions may make it harder to be organized enough to emigrate (see Cantor-Graae & Selten, 2005).

Perhaps the strongest clue comes from the finding that immigrants with darker skin have a much higher risk of developing schizophrenia than do immigrants with lighter skin (Cantor-Graae & Selten, 2005). This raises the possibility that experiences of being discriminated against could lead some immigrants to develop a paranoid and suspicious outlook on the world, which could set the stage for the development of schizophrenia. In support of this idea, the results of a prospective study show that healthy people who felt discriminated against were more likely to develop psychotic symptoms over time than were healthy people who did not perceive any discrimination (Janssen et al., 2003). Another possibility suggested by animal studies is that the stress that results from social disadvantage and social defeat may have an effect on dopamine release or dopamine activity in key neural circuits (Tidey & Miczek, 1996). Moreover, some of these biological changes could make people more sensitive to the effects of using illicit substances (Miczek et al., 2004). This is especially interesting in light of evidence linking cannabis abuse to the development of schizophrenia.

Immigration has been found to be a risk factor for developing schizophrenia. People who leave their native land to live in another country have almost three times the risk of developing schizophrenia compared to people who remain living in their home country. What factors may contribute to this increased risk?

Cannabis Use and Abuse

People with schizophrenia are twice as likely as people in the general population to smoke cannabis (van Os et al., 2002). This has prompted researchers to ask whether there is a causal link between cannabis abuse and the development of psychosis. A methodologically rigorous study of conscripts to the Swedish army shows that, compared to those who had never used cannabis, young men who were heavy cannabis users by the time they were 18 were more than six times more likely to have developed schizophrenia 27 years later (Zammit et al., 2002). This association also remained even after people who had used other kinds of drugs were removed from the statistical analysis.

Other studies have now replicated this link and have highlighted early cannabis use as being particularly problematic (see van Winkel & Kuepper, 2014, for a review). For example, Arsenault and colleagues (2002) report that 10.3 percent of those who used cannabis by age 15 were diagnosed with signs of schizophrenia by age 26, compared with only 3 percent of the controls who did not use cannabis. Taken together, the research findings suggest that using cannabis during adolescence more than doubles a person's risk of developing schizophrenia at a later stage of life.

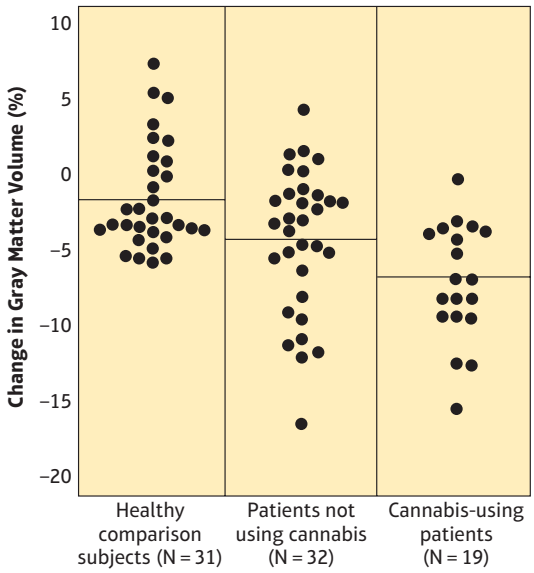
A major methodological concern in studies of this kind is whether people who are in the early stages of developing psychosis are more likely to use cannabis. If this were the case, cannabis use would simply be a correlate of schizophrenia and not a cause. However, even after childhood psychotic symptoms are considered and accounted for statistically, cannabis use has still been found to be a predictor of later schizophrenia (Fergusson et al., 2003). Moreover, a meta-analysis involving 8,167 patients with psychosis has shown that those who used cannabis (but not those who used alcohol) had an earlier onset of their symptoms compared to nonusers. These findings are consistent with the idea that cannabis use might trigger or bring forward the onset of psychosis (Large et al., 2011). This could be because one of the active ingredients of cannabis (called THC) increases dopamine in several areas of the brain (El Khoury et al., 2012). Cannabis also makes symptoms worse in patients who already have schizophrenia (D'Souza et al., 2005).

Of course, the vast majority of people who use cannabis do not develop schizophrenia. So can we predict who is at higher risk? Having a family history of schizophrenia may make people more sensitive to the psychosis-inducing effects of cannabis. And, in an early study, Caspi and colleagues (2005) reported that people carrying a particular form of the *COMT* gene (one or two copies of the valine or val allele) were at increased risk for developing psychotic symptoms (hallucinations or delusions) in adulthood if they used cannabis during adolescence. However, this link has proven difficult to replicate. Nonetheless, other gene–environment associations have been reported and a gene called *AKT1* is now a focus of interest (van Winkel & Kuepper, 2014). How everything fits together still remains to be discovered, however.

Finally, we note that there is some evidence that cannabis may actually accelerate the progressive brain changes that seem to go along with schizophrenia. Rais and colleagues (2008) collected brain scan data from 51 patients with recent-onset schizophrenia and 31 healthy controls. Nineteen of the patients were using cannabis (but not other illicit drugs) and 32 patients were not. When MRI scans were conducted again 5 years later, the patients who had continued to use cannabis during this time showed more marked decreases in brain volume relative to the patients who did not use cannabis. The changes in gray matter (brain cell) volume in the healthy controls, cannabis-using patients, and patients who did not use cannabis over the 5-year period are shown in Figure 13.10. Although both groups of patients lost more brain tissue over time than the healthy controls did, loss of brain tissue was especially pronounced in the patients who used cannabis. The conclusion is obvious. If you have schizophrenia, cannabis is probably very bad for your brain.

Figure 13.10 Brain Volume Changes over 5 Years in Patients with Schizophrenia and Healthy Comparison Subjects

Patients with schizophrenia who also use cannabis show more loss of gray matter over the course of a 5-year follow-up than patients who do not use cannabis or healthy controls.



A Diathesis–Stress Model of Schizophrenia

Biological factors undoubtedly play a role in the etiology of schizophrenia. But genetic predispositions can be shaped by environmental factors such as prenatal exposures, infections, and stressors that occur during critical periods of brain development (see Table 13.2 for a summary of nongenetic risk factors). Favorable environments may also reduce the chance that a genetic predisposition will result in schizophrenia. As we have discussed, children at genetic risk who are adopted into healthy family environments do very well (Tienari et al., 2004; Wahlberg et al., 1997). What you should take away from this chapter therefore is an understanding that schizophrenia is a genetically influenced, not a genetically determined, disorder (Gottesman, 2001).

Table 13.2 Nongenetic Risk Factors for Schizophrenia

Older father
Virus exposure
Obstetric complications
Urban upbringing
Head injury
Cannabis use
Migrant status

The diathesis–stress model, whose origins largely derive from schizophrenia research, predicts exactly these sorts of scenarios (e.g., Walker & Diforio, 1997; Zubin & Spring, 1977). Figure 13.11 provides a general summary of the interplay between genetic factors, prenatal events, brain maturational processes, and stress in the development of schizophrenia.

The bottom line is that there is no simple answer to the question of what causes schizophrenia. The etiology of this disorder (or group of related disorders) is complicated and complex. In the case of a person who develops schizophrenia, predisposing genetic factors must have combined in additive and interactive ways with multiple environmental risk factors, some known and some still unknown, that operate prenatally, perinatally, and also postnatally (see Gottesman, 2001; Walker & Tessner, 2008). The net result of this is that brain pathways develop abnormally. It is also very likely that these same pathways can be damaged in a host of different ways (in much the same way as a car engine can be damaged by lack of oil, lack of coolant, or from using the wrong kind of fuel). In other words, lots of roads may lead to the same end point, which is schizophrenia or a schizophrenia-like illness. This helps explain why past efforts to find the single cause of schizophrenia were doomed to fail, although no one could know this at the time. How we are born and how we live make major contributions. As one researcher has so aptly stated, "Schizophrenia may be the uniquely human price we pay as a species for the complexity of our brain; in the end, more or less by genetic and environmental chance, some of us get wired for psychosis" (Gilmore, 2010, p. 9).

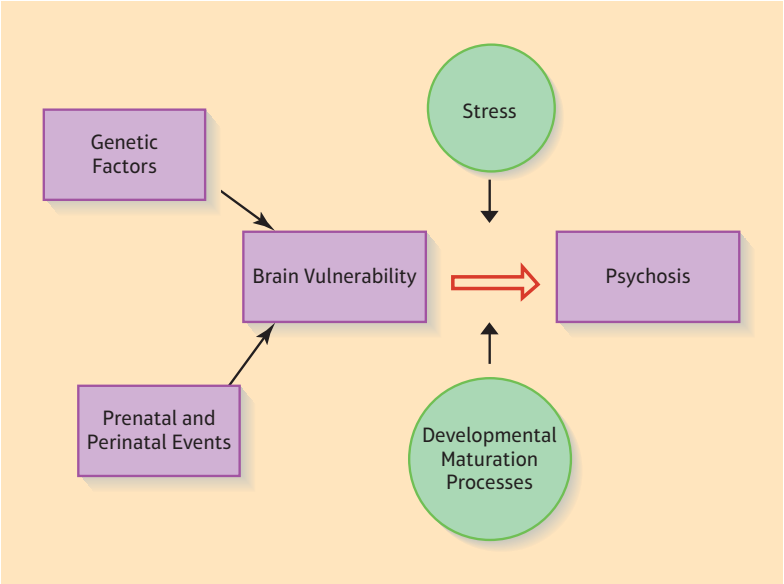


Figure 13.11 A Diathesis–Stress Model of Schizophrenia

Genetic factors and acquired constitutional factors (such as prenatal events and birth complications) combine to result in brain vulnerability. Normal maturational processes, combined with stress factors (family stress, cannabis use, urban living, immigration, etc.), may push the vulnerable person across the threshold and into schizophrenia.

in review

- What role does expressed emotion play in the relapse of schizophrenia?
- Why should immigration be associated with an elevated risk of schizophrenia?
- Why do we believe that schizophrenia is both a developmental and a neuroprogressive disorder?
- Why is the diathesis–stress perspective so appropriate for understanding schizophrenia?

Treatments and Outcomes

13.7 Describe the clinical outcome of schizophrenia and how is it treated, noting the advantages and disadvantages associated with the use of antipsychotic medications.

Before the 1950s the prognosis for schizophrenia was bleak. Treatment options were very limited. Agitated patients might be put in straitjackets or treated with electroconvulsive "shock" therapy. Most lived in remote and forbidding institutions that they were expected never to leave (Deutsch, 1948).

Dramatic improvement came in the 1950s when a class of drugs known as antipsychotics was introduced. Pharmacotherapy (treatment by drugs) with these medications rapidly transformed the environment of mental hospitals by calming patients and virtually eliminating their wild, dangerous, and out-of-control behaviors. A new and more hopeful era had arrived.

Clinical Outcome

Studies of clinical outcome show that 15 to 25 years after developing schizophrenia, around 38 percent of patients have a generally favorable outcome and can be thought of as being recovered (Harrison et al., 2001). This does not mean that patients return to how they were before they became ill, however. Rather, it means that with the help of therapy and medications, patients can function quite well. For a minority of patients (around 12 percent), long-term institutionalization is necessary. And around a third of patients show continued signs of illness, usually with prominent negative symptoms.

When more stringent criteria are used to define recovery (i.e., remission of symptoms and good general social functioning with improvements in at least one of these areas lasting 2 years or more), rates of recovery are even more modest. Recent estimates suggest that they are around 14 percent (Jääskeläinen et al., 2013). What this means is that, despite many advances in treatment during the past 50 to 60 years, a "cure" for schizophrenia has not materialized.

Interestingly, patients who live in less industrialized countries tend to do better overall than patients who live in more industrialized nations (Jablensky et al., 1992). This may be because levels of EE are much lower in countries such as India than in the United States and Europe. For example, in highly industrialized cultures, more than 50 percent of families are high in EE. In contrast, studies with Mexican American and Hindi-speaking Indian samples show that only 24 and 41 percent of families, respectively, are high in EE (see Karno et al., 1987; Leff et al., 1987). These differences may help explain why the clinical outcome of patients is different in different parts of the world.

Sometimes, patients who have been very severely impaired by schizophrenia show considerable improvement late in the course of their illness. As illustrated in the case that follows, these spontaneous improvements can occur even when there is no change in the medications that patients are taking.

From Impairment to Improvement

The patient is a 46-year-old man who first became ill when he was 17 years old. At the time his illness began, he was hearing voices and he had grandiose delusions. He also had delusions of being persecuted.

By the time he was 30, he was living in the hospital. He experienced continuous symptoms including delusions, hallucinations, and incoherent speech. His self-care was also very poor. His symptoms showed only minimal improvement after he was treated with clozapine.

Spontaneous clinical improvement was noted when the patient was in his 40s. He became less isolated and he began to spend more time doing activities. Although he had previously been incoherent when he spoke, he began to speak rationally, although there was still some poverty in the content of his speech. His self-care also improved. However, hospital staff still needed to prompt him to bathe and change his clothes. (Adapted from Murray et al., 2004.)

MORTALITY The health risks of having schizophrenia cannot be understated. This is a disorder that reduces life expectancy. Recent data from the United Kingdom show that men with schizophrenia die 14.6 years earlier than would be expected based on national norms. For women with schizoaffective disorder the reduction in life span is 17.5 years (Chang et al., 2011). Some of the factors implicated in the early deaths of patients with schizophrenia and schizophrenia-related illnesses are long-term use of antipsychotic medications, obesity, smoking, poor diet, use of illicit drugs, and lack of physical activity. The risk of suicide in patients with schizophrenia is also high compared to the general population, with about 12 percent of patients ending their lives in this way (Dutta et al., 2010). In general, overall mortality is lower in patients who are treated with antipsychotic medications compared to untreated patients (Tiihonen et al., 2011). This no doubt reflects the extent to which people who are actively psychotic are a risk to themselves.

Pharmacological Approaches

Medications are widely used in the treatment of schizophrenia. Over 60 different antipsychotic drugs have been developed. The common property that they all share is their ability to block dopamine D2 receptors in the brain (Seeman, 2011).

FIRST-GENERATION ANTIPSYCHOTICS First-generation **antipsychotics** are medications like chlorpromazine (Thorazine) and haloperidol (Haldol), which were among the first to be used to treat psychotic disorders. Sometimes referred to as **neuroleptics** (literally, "seizing the neuron"), these medications revolutionized the treatment of schizophrenia when they were introduced in the 1950s and can be regarded as one of the major medical advances of the twentieth century (Sharif et al., 2007). They are called first-generation antipsychotics (or typical antipsychotics) to distinguish them from a new class of antipsychotics that was developed much more recently. These are referred to as second-generation (or atypical) antipsychotics.

There is overwhelming evidence that antipsychotic medications help patients. Large numbers of clinical trials have demonstrated the efficacy and effectiveness of these drugs (Sharif et al., 2007). Also, the earlier patients receive these medications, the better they tend to do over the longer term (Marshall et al., 2005; Perkins et al., 2004). As we discussed earlier, first-generation antipsychotics are thought to work because they are dopamine antagonists. This means that they block the action of dopamine, primarily by blocking (occupying) the D2 dopamine receptors.

Some clinical change can be seen within the first 24 hours of treatment (Kapur et al., 2005). This supports the idea that these medications work by interfering with dopamine transmission at the D2 receptors because dopamine blockade begins within hours after a patient is given the medication. However, it may take several weeks or even months for maximal clinical benefit to be achieved, although how a patient does on a particular medication in the first 2 to 4 weeks of treatment is a good predictor of how much he or she will benefit overall (Tandon et al., 2010).

First-generation antipsychotics work best for the positive symptoms of schizophrenia. In quieting the voices and diminishing delusional beliefs, these medications provide patients with significant clinical improvement (Tandon et al., 2010). This comes at a cost, however. Common side effects of these medications include drowsiness, dry mouth, and weight gain. Many patients on these antipsychotics also experience what are known as *extrapyramidal side effects* (EPS). These are involuntary movement abnormalities (muscle spasms, rigidity, shaking) that resemble Parkinson's disease.

African Americans and other ethnic minorities appear to be at increased risk of extrapyramidal side effects (Lawson, 2008). Such side effects are usually controlled by taking other medications. Some patients who have been treated with neuroleptics for long periods of time may also develop *tardive dyskinesia*. This involves marked involuntary movements of the lips and tongue (and sometimes the hands and neck). Rates of tardive dyskinesia are about 56 percent when patients have taken neuroleptics for 10 years or more, with females being especially susceptible (Bezchlibnyk-Butler & Jeffries, 2003). Finally, in very rare cases there is a toxic reaction to the medication that is called *neuroleptic malignant syndrome*

(Strawn et al., 2007). This condition is characterized by high fever and extreme muscle rigidity, and if left untreated it can be fatal.

SECOND-GENERATION ANTIPSYCHOTICS In the 1980s a new class of antipsychotic medications began to appear. The first of these to be used clinically was clozapine (Clozaril). This drug was introduced in the United States in 1989, although clinicians in Europe had been using it prior to this. Although initially reserved for use with treatment-refractory patients (those who were not helped by other medications), clozapine is now used widely.

Other examples of second-generation antipsychotic medications are risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), and ziprasidone (Geodon). More recent additions include aripiprazole (Abilify) and lurasidone (Latuda). The reason why these medications are called "second-generation antipsychotics" is that they cause fewer extrapyramidal symptoms than the earlier antipsychotic medications such as Thorazine and Haldol. Although it was initially believed that second-generation antipsychotics were more effective at treating the symptoms of schizophrenia, recent research provides no support for this view (Lieberman & Stroup, 2011; Tandon et al., 2010). The exception here concerns clozapine, which does seem to be more valuable than other medications for treatment-refractory patients. Nonetheless, most patients are now treated with these newer (and more expensive) medications.

Although they are less likely to cause movement problems, the newer neuroleptic medications are not without other side effects. Drowsiness and considerable weight gain are very common. Diabetes is also a very serious concern (Sernyak et al., 2002). In rare cases, clozapine also causes a life-threatening drop in white blood cells known as agranulocytosis. For this reason, patients taking this medication must have regular blood tests.

The disappointing findings about the efficacy of second-generation antipsychotic treatments mean that there is an urgent need for innovative approaches and new medications that work better than the ones currently available. Antipsychotic medications work by blocking D2 receptors. But, as described earlier, researchers now believe that the most important dopamine abnormality in schizophrenia is occurring presynaptically. This means that current medications are working downstream from where the real problem may lie. Although antipsychotic medications do suppress dopamine neurotransmission overall (which is why they are helpful), future treatment developments that target the upstream abnormalities are clearly needed. This is all the more important in light of new research showing that current antipsychotic medications may actually contribute to the progressive brain tissue loss we see in schizophrenia (Ho et al., 2011). In the meantime, researchers continue to seek other ways to help patients.

OTHER APPROACHES At the beginning of the chapter, you learned that women with schizophrenia tend to do better than men. They have a later age of onset and, often, seem to have a less severe form of the illness. This has prompted some researchers to explore the potentially beneficial role of estrogen in the treatment of the disorder (Begemann et al., 2012).

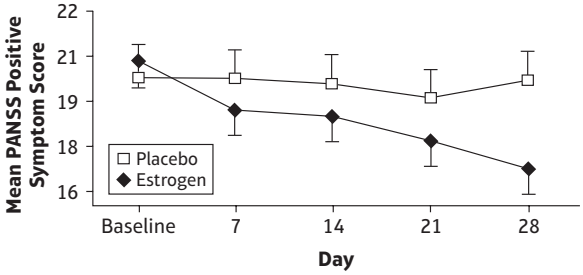
In an interesting study, 102 young women with schizophrenia (all of whom were receiving antipsychotic medications) were randomly assigned to one of two conditions (Kulkarni et al., 2008). Some were given a transdermal (skin) patch containing estrogen; the others received a similar (placebo) patch that contained no active ingredient. The women's symptoms were assessed at baseline. They then wore the patches for a period of 28 days, receiving new patches twice a week. At the end of the study period, symptoms were reassessed.

What were the findings? Remarkably, the women who had worn the genuine (estrogen-containing) patches reported significantly fewer overall symptoms at the end of the 1-month study compared to the placebo group, with the difference for positive symptoms (shown in Figure 13.12) being most striking. Overall, the results suggest that estrogen has antipsychotic effects and that providing supplemental estrogen to women with schizophrenia may give them additional clinical benefits.

Figure 13.12 Estrogen Treatment and Positive Symptoms

Positive symptoms at baseline (day 0) and on days 7, 14, 21, and 28 for the estrogen and placebo groups.

(Figure 3 from Kulkarni et al. (2008). *Archives of General Psychiatry*, *65*(8), 958 (Copyright © 2008). American Medical Association. Reprinted with permission.)



THE PATIENT'S PERSPECTIVE Not all patients benefit from antipsychotic medications, and many who do show clinical improvement will still have problems functioning without a great deal of additional help. We must also not lose sight of what it is like for patients with schizophrenia to have to take medications every day, often for years or for a lifetime. Side effects that can sound trivial to someone on the outside can be so bad for patients that they refuse to take their medications, even when those medications give them relief from their hallucinations and delusions.

Research using PET also shows that increased blockade of D2 dopamine receptors is associated with patients reporting more negative subjective experiences such as feeling tired and depressed even when other side effects (such as movement problems) are absent (Mizrahi et al., 2007). This highlights the need for better medications and for using lower dosages wherever this is clinically feasible. We also need to remember that some patients may try to avoid taking medications because, to them, needing to take medications confirms that they are mentally ill. The following comes from the mother of a daughter who suffers from schizophrenia:

> As a parent I also know that medication is not perfect and that the side effects can be distressing. When my daughter goes back on her medication, I feel bad seeing her shuffling or experiencing involuntary arm and mouth movements. These symptoms usually subside over time; but she also gains weight, and she hates being heavy. I think she hates taking medication most of all because she is, in a sense, admitting she is mentally ill, something she very much wants to deny. (From Slater, 1986.)

Psychosocial Approaches

Medications play a central role in the treatment of schizophrenia. But they are not the only treatment approaches that are available. Psychosocial treatments are also of value. Some of these approaches, which are typically used in conjunction with medication, are briefly described below.

FAMILY THERAPY The literature that links relapse in patients with schizophrenia to high family levels of EE inspired several investigators to develop family intervention programs. The idea was to reduce relapse in schizophrenia by changing those aspects of the patient–relative relationship that were regarded as central to the EE construct. At a practical level, this generally involves working with patients and their families to educate them about schizophrenia, to help them improve their coping and problem-solving skills, and to enhance communication skills, especially the clarity of family communication.

In general, the results of research studies in this area have shown that patients do better clinically and relapse rates are lower when families receive family treatment (see Pfammatter et al., 2006). Studies done in China indicate that these treatment approaches can also be used in other cultures (Xiong et al., 1994). Despite this, family treatment is still not a routine element in the accepted standard of care for patients with schizophrenia (Lehman et al., 1998). Given its clear benefits to patients and its considerable cost effectiveness (Tarrier et al. [1991] calculated that family treatment results in an average cost savings of 27 percent per patient), this seems very unfortunate. This is even more so in light of new evidence showing that extended periods of relapse predict increased loss of brain tissue over time (Andreasen et al., 2013). Preventing relapse is therefore of paramount importance.

CASE MANAGEMENT Case managers are people who help patients find the services they need in order to function in the community. Essentially, the case manager acts as a broker, referring the patient to the people who will provide the needed service (e.g., help with housing, treatment, employment, and the like). Assertive community treatment programs are a specialized and more intensive form of case management. Typically, they involve multidisciplinary teams with limited caseloads to ensure that discharged patients don't get overlooked and "lost in the system." The multidisciplinary team delivers all the services the patient needs (see DeLuca et al., 2008; Mueser et al., 2013).

Assertive community treatment programs are cost effective because they reduce the time that patients spend in the hospital. They also enhance the stability of patients' housing arrangements. These approaches seem to be especially beneficial for patients who are already high utilizers of psychiatric and community services (see Bustillo et al., 2001).

SOCIAL-SKILLS TRAINING Even when their symptoms are controlled by medications, patients with schizophrenia often have trouble forming friendships, finding and keeping a job, or living independently. How well patients do in their everyday lives is referred to as *functional outcome*. (This is in contrast to *clinical outcome*, which is concerned with symptoms.) Improving the functional outcomes of patients with schizophrenia is now an active area of research.

One way to help improve the functional outcomes of patients with schizophrenia is through social-skills training. Patients with schizophrenia often have very poor interpersonal skills (for a review, see Hooley, 2015). Social-skills training is designed to help patients acquire the skills they need to function better on a day-to-day basis. These skills include employment skills, relationship skills, self-care skills, and skills in managing medications or symptoms. Social routines are broken down into smaller, more manageable components. For conversational skills, these components might include learning to make eye contact, speaking at a normal and moderate volume, taking one's turn in a conversation, and so on. Patients learn these skills, get corrective feedback, practice their new skills using role-playing, and then use what they have learned in natural settings (Bellack & Mueser, 1993). As Green (2001, p. 139) has noted, engaging in social-skills training is a bit like taking dance lessons. It does not resemble traditional "talk therapy" in any obvious manner.

Although the results of some early studies were mixed, the most recent research findings look more positive. Social-skills training does seem to help patients acquire new skills, be more assertive, and improve their overall levels of social functioning. These improvements also seem to be maintained over time. Importantly, patients who

receive social-skills training are less likely to relapse and need hospital treatment (Kurtz & Mueser, 2008; Pfammatter et al., 2006).

An even newer treatment approach is social cognitive skills training. This is designed to improve the deficits in social cognition we described earlier. For example, patients might be trained to recognize emotion in faces or to better recognize hints. The early findings suggest that these interventions do provide benefits to patients and help them function better in the community. However, positive and negative symptoms show little change (Kurtz & Richardson, 2012).

COGNITIVE REMEDIATION Earlier we described some of the cognitive problems that go along with having schizophrenia. Researchers are now recognizing that these cognitive problems are likely to place limits on how well patients can function in the community. Because of this, the neurocognitive deficits of schizophrenia are becoming targets for treatment in their own right. The search is on to develop new medications that will enhance cognitive functioning in patients (Green, 2007; Nuechterlein et al., 2008).

A major treatment effort is also being devoted to **cognitive remediation** training. Using practice and other compensatory techniques, researchers are trying to help patients improve some of their neurocognitive deficits (e.g., problems with verbal memory, vigilance, and performance on card-sorting tasks). The hope is that these improvements will translate into better overall functioning (e.g., conversational skills, self-care, and job skills). Overall, the findings give cause for optimism. Cognitive remediation training does seem to help patients improve their attention, memory, and executive functioning skills. Patients who receive cognitive remediation training also show improvements in their social functioning. Especially encouraging is that even when patients have been ill for many years, they still seem to benefit from this treatment approach (Pfammatter et al., 2006; Wykes et al., 2007). Cognitive remediation approaches may work best when they are added to other existing rehabilitation (employment skills) strategies and offered to patients who are already clinically stable (Wykes et al., 2011).

Patients with schizophrenia benefit from psychosocial treatments. These include individual therapy, case management, cognitive remediation, and family therapy.

COGNITIVE-BEHAVIOR THERAPY As you have already learned, cognitive-behavior therapy (CBT) approaches are widely used in the treatment of mood and anxiety disorders as well as many other conditions (Beck, 2005). Until fairly recently, however, researchers did not consider using them for patients with schizophrenia, no doubt because patients with schizophrenia were considered too impaired. Pioneered by researchers and clinicians in the United Kingdom, cognitive-behavior approaches have gained momentum in the treatment of schizophrenia. The goal of these treatments is to decrease the intensity of positive symptoms, reduce relapse, and decrease social disability. Working together, therapist and patient explore the subjective nature of the patient's delusions and hallucinations, examine evidence for and against their veracity or veridicality, and subject delusional beliefs to reality testing.

Although the results from the early research studies were encouraging, whether CBT is an effective treatment for schizophrenia is now the subject of some debate. Current data suggest that CBT is not very helpful for negative symptoms (Tandon et al., 2010). A recent meta-analysis also suggests that CBT is no better than control interventions (often supportive counseling) in the treatment of schizophrenia (Lynch et al., 2010). Nonetheless, the possibility that CBT works very well for some subgroups of patients is still a very real possibility.

INDIVIDUAL TREATMENT Before 1960 the optimal treatment for patients with schizophrenia was psychoanalytically oriented therapy based on a Freudian type of approach. This is what Nobel Prize–winning mathematician John Nash (who died in a car crash in 2015) received when he was a patient at McLean Hospital in Massachusetts in 1958 (the movie *A Beautiful Mind,* is based on Nash's story). By 1980, however, things had changed. Research began to suggest that in some cases, psychodynamic treatments made patients worse (see Mueser & Berenbaum, 1990). This form of individual treatment thus fell out of favor.

Individual treatment for schizophrenia now takes a different form. Hogarty and colleagues (1997a, 1997b) have reported on a controlled 3-year trial of what they call "personal therapy." Personal therapy is a nonpsychodynamic approach that equips patients with a broad range of coping techniques and skills. The therapy is staged, which means that it comprises different components that are administered at different points in the patient's recovery. For example, in the early stages, patients examine the relationship between their symptoms and their stress levels. They also learn relaxation and some cognitive techniques. Later, the focus is on social and vocational skills. Overall, this treatment appears to be very effective in enhancing

the social adjustment and social role performance of discharged patients.

Educating patients about the illness and its treatment (this approach is called psychoeducation) is also helpful (Xia et al., 2011). Patients who receive psychoeducation in addition to standard treatment are less likely to relapse or be readmitted to the hospital compared to patients who receive standard treatment only. These patients also function better overall and are more satisfied with the treatment they receive. All of this highlights the importance of including patients in their own care and increasing their knowledge and understanding about their illness.

In summary, although rigorous psychoanalytic approaches may be too demanding and stressful for patients with schizophrenia, supportive forms of therapy that offer an opportunity to learn skills and yet are low key and responsive to patients' individual concerns might well be very beneficial. Just as progress in research on schizophrenia requires a partnership between scientists across many areas, progress in the treatment of schizophrenia requires balancing pharmacology with a consideration of the specific needs of the patient. For patients who are at high risk of relapse and who live with their families, family-based interventions will be required. If patients have continuing and disturbing hallucinations and delusions, CBT may be appropriate. When patients are clinically stable, social-skills or social-cognitive training and rehabilitation efforts may be helpful. But in all of this, we must not lose sight of the need of patients (and their families) for support, validation, and respectful care. The treatment of patients with schizophrenia is not easy, and there is no "quick fix." Although many treatment advances have occurred, we still need more effective, high-quality, and clinically sensitive care.

in review

- What kinds of clinical outcomes are associated with schizophrenia? Is full recovery possible or typical?
- Why do patients with schizophrenia have increased rates of early mortality?
- In what ways are first- and second-generation (conventional and atypical) neuroleptic medications similar, and in what ways are they different? How effective are these treatments for patients with schizophrenia?
- Describe the major psychosocial approaches used in treating schizophrenia.

Unresolved Issues

Why Are Recovery Rates in Schizophrenia Not Improving?

After the introduction of the first neuroleptic medication (Thorazine) in 1955, there was great optimism that this, and other new "wonder drugs," would revolutionize the treatment of schizophrenia. Today, many decades later, clinicians have a broad array of first- and second-generation antipsychotic medications at their disposal. But if our treatment options are so much more sophisticated, why are recovery rates in schizophrenia so low?

The standard length of a clinical trial that compares a given drug against a placebo is 6 weeks. Numerous clinical studies have demonstrated that antipsychotic medications are effective for the treatment of acute symptoms. So there is little doubt that antipsychotic medications benefit patients in the short term. But what about the longer term? Does staying on antipsychotic medications provide long-term benefits for patients?

The answer may be no. Concerns are now being raised that long-term exposure to neuroleptics may set into play biological process that increase the likelihood that patients will remain chronically ill (Whitaker, 2010). This is particularly worrisome because patients who take neuroleptic medications tend to stay on them for very long periods of time.

But how could something that is clinically beneficial in the short term be potentially harmful in the longer term? Standard antipsychotic medications block D2 receptors in the brain. This is the basis of their therapeutic action. But one result of dopamine blockade is that the density of receptors on the postsynaptic neuron increases, creating a supersensitivity to dopamine. Put more simply, neuroleptics put a brake on dopamine transmission. To compensate for this, the brain responds by pressing the dopamine accelerator (in the form of extra dopamine receptors). Withdrawal of neuroleptics removes the brake and puts the system out of balance because the system is now in an "accelerator-on" mode. Moreover, any return of symptoms is taken as evidence that the drugs were working and preventing relapse. This impression gets confirmed when the patient goes back on drugs again and the psychosis abates. As one physician noted, "The use of neuroleptics is a trap. . . . It is like having a psychosis-inducing agent built into the brain." (Whitaker, 2010, pp. 107).

As you might expect, the idea that antipsychotic medications may help psychosis in the short term but create it in the longer term is highly controversial. However, it may not be as far fetched as it might seem. Data from a 20-year follow-up study show that over time, patients with schizophrenia who are not taking antipsychotic medications fare far better than those who continue to take medications (Harrow et al., 2012). Of the patients who took antipsychotic medications continuously during the follow-up study period, only 17 percent had a period of recovery at some point. In contrast, 87 percent of the patients who had gone off antipsychotic medications before the 2-year follow-up assessment were rated as being recovered at two or more or the follow-up assessments. Differences in recovery rates between the medicated and unmedicated groups began to be apparent at the 4.5-year follow-up. At that assessment, and also at all subsequent follow-up visits, the unmedicated patients were doing better.

Can we attribute the poor clinical outcomes of the medicated patients to the continued use of antipsychotics? Harrow and colleagues (2012) suggest not. Rather, they suggest that the difference between the medicated and unmedicated groups exists because the patients who go off antipsychotics have other resources and strengths that eventually lead them to have a better long-term prognosis. So the patients with the most favorable clinical outcomes stop taking medications and the patients with the least favorable clinical outcomes keep taking medications. This may be so. But it is interesting that many of the patients who stopped taking their medications did so against professional advice. So, if these patients were somehow more resilient and destined to do better, their psychiatrists apparently did not recognize it.

It is also the case that patients who stop taking medications tend not to see their psychiatrists. So clinicians don't see people who recover. This may be one reason why psychiatry as a whole has been slow to recognize that nonmedicated patients might be doing far better than expected. Also relevant here is the observation that patients in less industrialized countries tend to do better clinically than those in more developed countries. And these are the very patients who are much less likely to be maintained on antipsychotic medications.

Perhaps most provocative are the following statistics about chronic mental illness. In 1955 one in every 617 Americans was hospitalized with schizophrenia in a state or county mental hospital. These were chronic long-term patients. Today, the proportion of people with chronic schizophrenia or some other psychotic disorder is much higher—1 in every 125 people. In his efforts to understand why psychiatric medications have not improved the long-term clinical outcomes for patients with severe mental illness, Whitaker (who is an investigative reporter) has caused a storm of controversy. Nonetheless, his arguments warrant serious consideration by all mental health professionals. If the medications that are so helpful in a crisis make things worse when used long term, we need to radically rethink how we manage the treatment of patients with schizophrenia. Based on the findings of Harrow et al. (2012), perhaps the most powerful conclusion that can be drawn at this stage is that not all patients with schizophrenia need to be treated long term with medications. When patients are motivated to try a period without antipsychotics, medical professionals might do well to support this decision.

Summary

13.1 Describe the prevalence of schizophrenia and who is most affected.

Schizophrenia affects just under 1 percent of the population. Most cases begin in late adolescence or early adulthood. The disorder begins earlier in men than in women. Overall, the clinical symptoms of schizophrenia tend to be more severe in men than in women. Women also have a better long-term outcome.

13.2 Identify the symptoms of schizophrenia as described in *DSM-5*.

Schizophrenia is the most severe form of mental illness. It is characterized by impairments in many domains. Characteristic symptoms of schizophrenia include hallucinations, delusions, disorganized speech, disorganized and catatonic behavior, and negative symptoms such as flat affect or social withdrawal.

13.3 List four different types of psychotic disorders and state one way in which each is different from schizophrenia.

- Other types of psychotic disorders are schizoaffective disorder, schizophreniform disorder, delusional disorder, and brief psychotic disorder.
- Schizoaffective disorder is a mix of symptoms of schizophrenia *and* mood disorder symptoms.
- In schizophreniform disorder, the clinical picture is like that of schizophrenia apart from the fact that the symptoms have not lasted long enough (6 months) to qualify for a diagnosis of schizophrenia.
- In delusional disorder, delusions are present but the person may otherwise behave quite normally. In other words, there is no sign of the gross disorganization and performance deficiencies that are associated with schizophrenia.
- Finally, brief psychotic disorder is very short lived. It involves the sudden onset of psychotic symptoms, disorganized speech, or catatonic behavior. Although the person may be quite impaired, the duration of this impairment is very brief (and too short to allow for a diagnosis of schizophreniform disorder). The person typically returns to his or her former level of functioning within a few days.

13.4 Explain the genetic and biological risk and causal factors associated with schizophrenia.

- Genetic factors are clearly implicated in schizophrenia. Many genes, each having a small effect are likely involved, as well as some rare alleles. Having a relative with the disorder significantly raises a person's risk of developing schizophrenia.
- Other factors that have been implicated in the development of schizophrenia include prenatal exposure to

viruses, rhesus incompatibility, pregnancy and birth complications, early nutritional deficiencies, maternal stress, maternal inflammation, and head injury.

13.5 Discuss how the brain is affected in schizophrenia.

- Patients with schizophrenia have problems in many aspects of their cognitive functioning. They show a variety of attentional deficits (e.g., poor P50 suppression and deficits on the Continuous Performance Test). They also show eye-tracking dysfunctions.
- Even though schizophrenia first shows itself clinically in early adulthood, researchers believe that it is a neurodevelopmental disorder. Problems with brain development are implicated. Some of the genes implicated in schizophrenia play a role in brain development.
- Many brain areas are abnormal in schizophrenia, although abnormalities are not found in all patients. The brain abnormalities that have been found include enlarged ventricles (which reflects decreased brain volume), frontal lobe dysfunction, reduced volume of the thalamus, and abnormalities in temporal lobe areas such as the hippocampus and amygdala.
- Major changes in the brain occur during adolescence. These include synaptic pruning, decreases in the number of excitatory neurons, and increases in the number of inhibitory neurons. There is also an increase in white matter, which enhances the connectivity of the brain. Some of these changes may be abnormal in people who will later develop schizophrenia.
- The most important neurotransmitters implicated in schizophrenia are dopamine and glutamate. Research shows that the people with schizophrenia may be producing and releasing too much dopamine into the synapse.
- Some of the brain abnormalities that are characteristic of schizophrenia get worse over time. This suggests that, in addition to being a neurodevelopmental disorder, schizophrenia is also a neuroprogressive disorder. Antipsychotic medications explain some (but not all) of the brain tissue loss.

13.6 Explain the psychosocial and cultural factors associated with schizophrenia.

- Urban living, immigration, and cannabis use during adolescence have also been shown to increase the risk of developing schizophrenia.
- Current thinking about schizophrenia emphasizes the interplay between genetic and environmental factors.

13.7 Describe the clinical outcome of schizophrenia and how is it treated, noting the advantages and disadvantages associated with the use of antipsychotic medications.

- For many patients, schizophrenia is a chronic disorder requiring long-term treatment or institutionalization. However, when treated with therapy and medications, around 38 percent of patients can show a reasonable recovery. Only about 14 percent of patients recover to the extent that they have minimal symptoms and function well socially.
- Patients with schizophrenia are more likely to relapse if their relatives are high in expressed emotion (EE). High-EE environments may be stressful to patients and may trigger biological changes that cause dysregulations in the dopamine system. This could lead to a return of symptoms.
- Treatment often involves first- or second-generation antipsychotic (neuroleptic) medications. Second-generation antipsychotics are about as effective as first-generation antipsychotics but cause fewer extrapyramidal (motor abnormality) side effects. Antipsychotic drugs work by blocking dopamine receptors. Some evidence suggest antipsychotic medications may be linked to brain tissue loss.
- Psychosocial treatments for patients with schizophrenia include social-skills training, social-cognitive training, cognitive remediation training, cognitive-behavior therapy, and other forms of individual treatment, as well as case management. Family therapy provides families with communication skills and other skills that are helpful in managing the illness. Family therapy also reduces high levels of expressed emotion.

Key Terms

alogia, p. 490
antipsychotics (neuroleptics), p. 520
attenuated psychosis syndrome, p. 504
avolition, p. 490
blunted affect, p. 490
brief psychotic disorder, p. 492
candidate genes, p. 498
catatonic schizophrenia, p. 491
cognitive remediation, p. 523
delusion, p. 486
delusional disorder, p. 492
disorganized schizophrenia, p. 491
dopamine, p. 512
endophenotypes, p. 499
expressed emotion (EE), p. 515
flat affect, p. 490
genome-wide association study (GWAS), p. 498
glutamate, p. 513
hallucination, p. 488
negative symptoms, p. 490
paranoid schizophrenia, p. 491
positive symptoms, p. 490
prodromal, p. 504
psychosis, p. 484
schizoaffective disorder, p. 491
schizophrenia, p. 484
schizophreniform disorder, p. 491