...compulsive disorders.

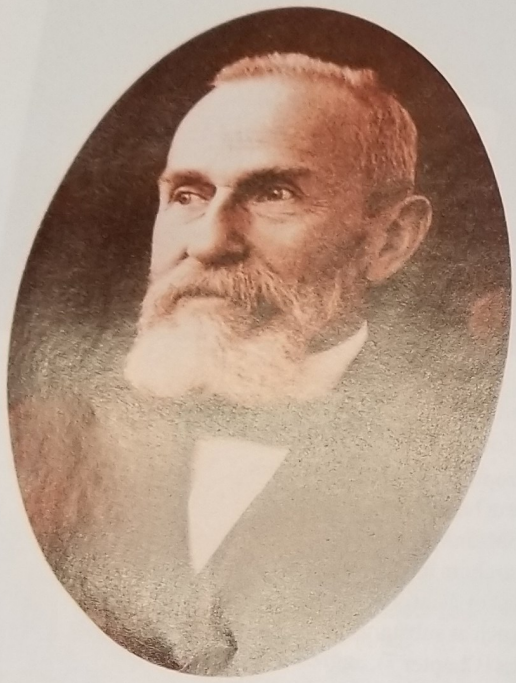
Schizophrenia

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

Characteristics of the Disorder

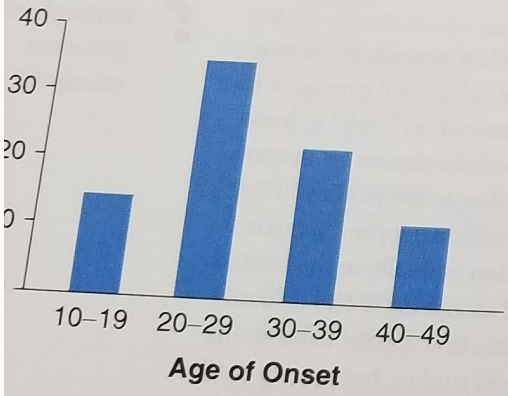
The term *schizophrenia* was coined in 1911 by the Swiss psychiatrist Eugen Bleuler (Figure 14.2) from the combination of two Greek words meaning "split mind." Contrary to popular belief, schizophrenia has

FIGURE 14.2 Eugen Bleuler (1857–1939).
A pioneer in the field, he introduced the term *schizophrenia*.



ource: © Bettmann/Getty Images.

FIGURE 14.3 Risk for Schizophrenia by Age.



rom Huber et al. (1980).

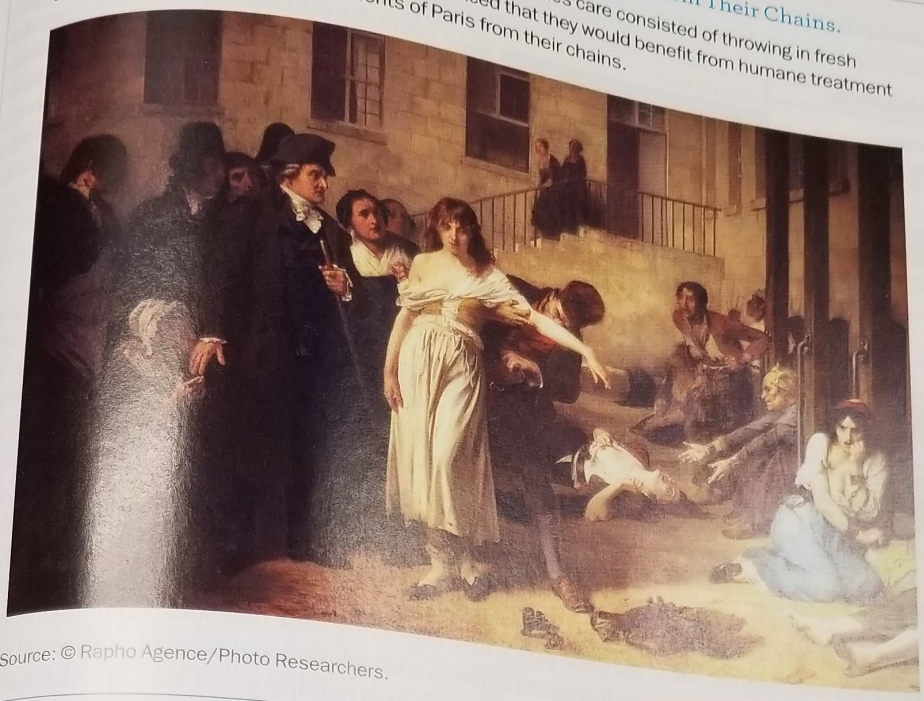
nothing to do with multiple personalities; the term refers to the distortion of thought and emotion, which are "split off" from reality. The schizophrenic has some combination of several symptoms: hallucinations (internally generated perceptual experiences, such as voices telling the person what to do);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

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

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

In the late 1700s and early 1800s, doctors began to view mental illness as a medical problem; at that time, the mentally ill were literally released from their chains and given treatment (Figure 14.4; Andreasen, 1984). By the early 20th century, it was widely assumed that schizophrenia had a physiological basis. But when the search for biological causes produced little success, the emphasis shifted in the 1940s to the social causes of schizophrenia, especially in America, where Freud's theory of psychoanalysis was in its ascendancy and biologically oriented psychiatrists were in the minority (Andreasen; Wender, Rosenthal, Kety, Schulsinger, & Welner, 1974). Until the 1960s, research techniques were not up to the task of demonstrating the validity of the physiological position. It was then that increasing knowledge of neurotransmitters, the advent of brain scanning techniques, and improved genetic studies shifted the explanation for schizophrenia back to the realm of biology and permanently changed the perception of mental illness.

FIGURE 14.4 Philippe Pinel Freeing Mental Patients From Their Chains.
Patients were warehoused without treatment; sometimes care consisted of throwing in fresh straw and food once a week. Pinel was convinced that they would benefit from humane treatment and in 1794 freed the mental patients of Paris from their chains.



Source: © Rapho Agence/Photo Researchers.

> "I'm a paranoid schizophrenic and for us life is a living hell. . . . Society is out to kill me. . . . I tried to kill my father. I went insane and thought he ruled the world before me and caused World War Two."
>
> —Ross David Burke in When the Music's Over: My Journey Into Schizophrenia

Heredity

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

Twin and Adoption Studies

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

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

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

FIGURE 14.5 Concordances for Schizophrenia Among Relatives.

Genetic Relatedness	Relationship	Risk
100%	Identical twin	48%
—	Offspring of two patients	46%
50%	Fraternal twin	17%
50%	Offspring of one patient	17%
50%	Sibling	9%
25%	Nephew or niece	4%
0%	Spouse	2%
0%	Unrelated person in the general population	1%

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

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

The Search for the Schizophrenia Genes

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

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

Schizophrenia is a very old disease (see W. J. Ray, 2014, for a review). Disorders with psychotic-like symptoms have been reported for 4,000 years, and similar rates in disparate and long-separated societies suggest that the genes were present before humans left Africa some 100,000 years ago. So why wouldn't genes as detrimental as those that produce schizophrenia be eliminated through evolution? One suggestion is that the genes that in combination can produce schizophrenia individually confer an evolutionary

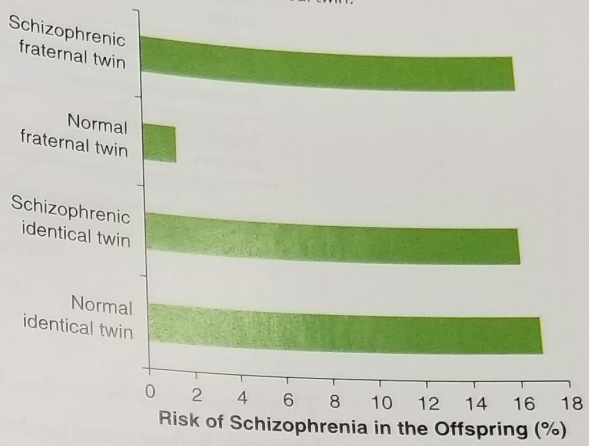
advantage. Ten or fifteen centuries ago, these individual genes might have helped individuals cope with the demands of burgeoning social culture. It has been pointed out that many gifted Nobel recipients, the likes of Albert Einstein, Bertrand Russell, and John Nash (featured in the film *A Beautiful Mind*), either had some schizophrenic traits or had relatives thought to have schizophrenia. In addition, an individual's overall risk for schizophrenia (as well as for bipolar disorder) is highly correlated with intellectual and artistic creativity (Power et al., 2015). Therefore, our amazing human ability to express, integrate, and create comes with an increased risk for psychotic disorders that can be triggered by the same genes and circuits.

The Vulnerability Model

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

FIGURE 14.6 Risk of Schizophrenia in the Offspring of Normal and Schizophrenic Twins.

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



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

Two Kinds of Schizophrenia

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

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

> "What consoles me is that I am beginning to consider madness as an illness like any other, and that I accept it as such.
>
> —Vincent van Gogh, 1889, in a letter to his brother, Theo

TABLE 14.2 Positive Versus Negative Schizophrenia.

ASPECT	TYPE I (POSITIVE)	TYPE II (NEGATIVE)
Characteristic symptoms	Delusions, hallucinations, etc.	Poverty of speech, lack of affect, etc.
Response to antidopaminergic drugs	Good	Poor
Symptom outcome	Potentially reversible	Irreversible?
Intellectual impairment	Absent	Sometimes present
Suggested pathological process	Increased D_2 dopamine receptors	Cell loss in temporal lobes

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

The Dopamine Hypothesis

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

So, investigators tried reverse engineering. You will remember from Chapter 5 that amphetamine overdose causes psychotic behavior indistinguishable from schizophrenia, complete with hallucinations and paranoid delusions. In time, researchers determined that amphetamine produces these symptoms by increasing dopaminergic activity. This discovery eventually led to the *dopamine hypothesis*, that schizophrenia involves excessive dopamine activity in the brain. According to the theory, blockade of the D_2 type of dopamine receptors is essential for a drug to have an antipsychotic effect, and a drug's effectiveness is directly related to the drug's blocking potency. The theory has considerable support; schizophrenic patients typically have higher dopamine activity in the striatum (Abi-Dargham et al., 2000), and drugs that block dopamine receptors are effective in treating the positive symptoms of schizophrenia (S. H. Snyder, Bannerjee, Yamamura, & Greenberg, 1974). In fact, the effective dosage for most antipsychotic drugs is directly proportional to their ability to block dopamine receptors (Figure 14.7; Seeman, Lee, Chau-Wong, & Wong, 1976). What exactly does dopamine do to trigger the symptoms of schizophrenia? One theory, called the *aberrant salience hypothesis*, suggests that heightened levels of dopamine increase attentional and motivational circuits to make ordinary environmental features seem significant. Therefore, an individual projects his or her own thoughts and imaginings as real-world events and experiences (Howes & Nour, 2016).

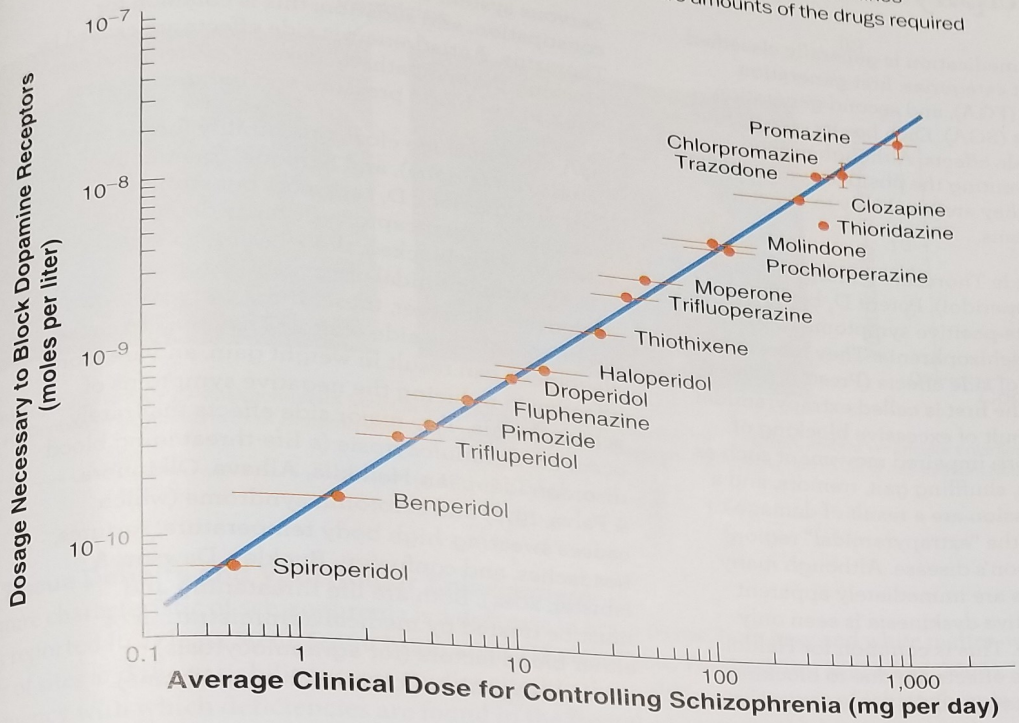
Beyond the Dopamine Hypothesis

However, the drugs did not help 30%–40% of schizophrenic patients, and—troublesome for the dopamine theory—nonresponsive patients experienced just as much D_2 receptor blockade as responders. In fact, in some of them the blockade exceeded 90%, while some responders showed remarkably low levels of receptor blocking (Kane, 1987; Pilowsky et al., 1993). Furthermore, some patients appear to have a *dopamine deficiency*, especially those with chronic, treatment-resistant symptoms (Grace, 1991; Heritch, 1990; Okubo et al., 1997).

Another problem for the drugs was that the side effects could be permanently disabling. Prolonged use of antidopamine drugs often produces *tardive dyskinesia*, tremors and involuntary movements due to long-term blocking of dopamine receptors and resultant neuron death in the basal ganglia. Once dyskinesia

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

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



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

develops, it persists even after the person stops taking the drug. Seventy years ago, this effect was believed to be so inevitably linked to the therapeutic benefit that the "right" dose was the one that caused some degree of motor side effects. Thus, the drugs used to treat schizophrenia became known as *neuroleptics,* because the term means "to take control of the neuron" (Julien, 2008). The effect appears to be due to a compensatory increase in the sensitivity of D_2 receptors in the basal ganglia. (This is a good illustration of the fact that drugs do not affect just the part of the brain we want to treat.)

Since the early 1990s, we have seen the introduction of several new antipsychotic substances that are referred to as *atypical* or *second-generation* drugs. Atypical antipsychotics block D_2 receptors less strongly, while also targeting non-dopamine receptors; as a result, they produce motor problems only at much higher doses, but they still reduce psychotic symptoms. Fortunately, avoiding motor side effects does not require a therapeutic compromise. The major atypical antipsychotics are at least equivalent to the first-generation drugs, and some are 15%–25% more effective; what is more, they often bring relief to treatment-resistant patients (Iqbal & van Praag, 1995; Leucht et al., 2009; Pickar, 1995; Siever et al., 1991). So, is the dopamine hypothesis just another example of a beautiful hypothesis slain by ugly facts? Not entirely; although atypical antipsychotics mostly target other receptors, those that lack at least a modest effect at D_2 receptors are therapeutically ineffective (H. M. Jones & Pilowsky, 2002). So, successful therapy apparently requires D_2 blockade *and* other effects. For a summary of the types of drugs prescribed for individuals with schizophrenia, and their side effects, see the accompanying Research Spotlight.

And what are these other effects? One involves serotonin. The serotonergic system is suspect largely because of the $5\text{-}HT_{2A}$ receptor's involvement in schizophrenic-like responses to hallucinogenic drugs, such as psilocybin and LSD. The number of $5\text{-}HT_{2A}$ receptors is upregulated in the brains of deceased schizophrenic subjects (González-Maeso et al., 2008), and atypical antipsychotics block serotonin $5\text{-}HT_2$ receptors by as much as 90%

RESEARCH SPOTLIGHT

Antipsychotics and Their Side Effects

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

FGA drugs include Thorazine (chlorpromazine) and Haldol (haloperidol). Potent D_2 blockers, they help alleviate positive symptoms in most individuals with schizophrenia. They have four major categories of side effects (Preston, O'Neal, & Talaga, 2013). The first is called extrapyramidal effects and is a result of excessive blocking of dopamine receptors; impaired movement such as tardive dyskinesia, shuffling gait, tremors, and a blank facial expression are a result of damage to the basal ganglia (the "extrapyramidal" region) and mimic Parkinson's disease. Although many of these side effects are immediately apparent with FGAs, the tardive dyskinesia is seen only after prolonged use. This is common for Haldol. Anticholinergic side effects are due to blocking acetylcholine receptors and the parasympathetic nervous system and includes dry mouth and eyes, constipation, and sedation; this is common for Thorazine. Antiadrenergic side effects are caused by blocking the sympathetic nervous system and can result in low blood pressure and lightheadedness.

SGA drugs include clozapine, Abilify (aripiprazole), Latuda (lurasidone), and Seroquel (quetiapine). They weakly block D_2 receptors but strongly block serotonin receptors. Because dopamine is not strongly blocked, there is a much smaller risk of extrapyramidal effects and tardive dyskinesia. However, these drugs carry their own set of undesirable side effects. They tend to cause sleepiness, can result in weight gain, and are more effective in reducing the negative symptoms of schizophrenia. Two major side effects that rarely occur are agranulocytosis (a life-threatening blood disorder; Idänpään-Heikkilä, Alhava, Olkinuora, & Palva, 1977) and serotonin syndrome (which causes sweating, high body temperature, seizures, headaches, and confusion; Buckley, Dawson, & Isbister, 2014). Both are life threatening and must be treated by medical administration of either blood factors (for agranulocytosis) or serotonin agonists (for serotonin syndrome).

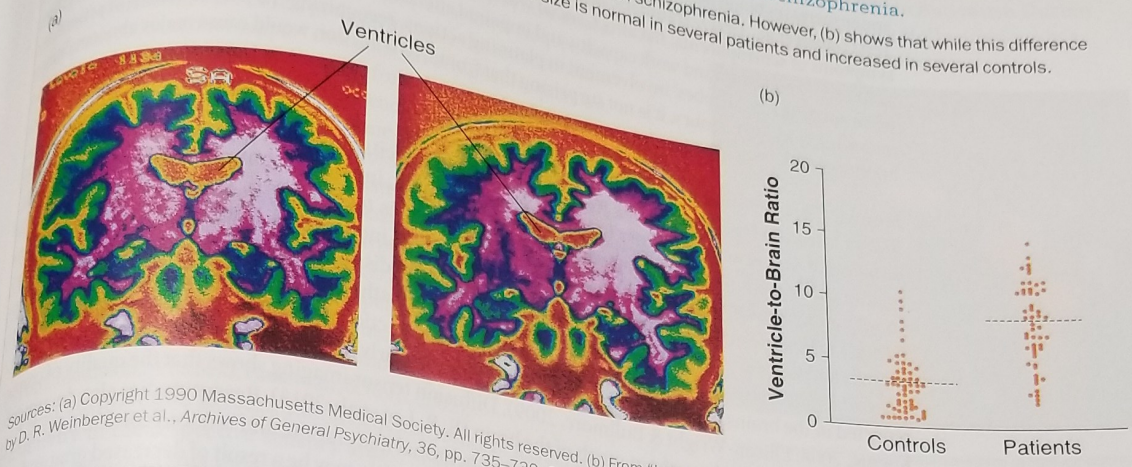
(H. M. Jones & Pilowsky, 2002; Kapur, Zipursky, & Remington, 1999). But serotonin has not received nearly as much attention as glutamate activity, which also is affected by atypical antipsychotics. The drug phencyclidine (PCP), which inhibits the NMDA (*N*-methyl-d-aspartic acid) subtype of glutamate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

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

Brain Anomalies in Schizophrenia

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

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



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

Brain Tissue Deficits and Ventricular Enlargement

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

? What brain defects have been found in schizophrenia?

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

Hypofrontality

Earlier, we saw that prefrontal functioning can be assessed by using the gambling task; an alternative technique is the *Wisconsin Card Sorting Test*, which requires individuals to change strategies in midstream, first sorting cards using one criterion but then changing to another. Many people with schizophrenia perform poorly on the test, persisting with the previous sorting strategy. Normal individuals show increased activation in the prefrontal area during the test; schizophrenic patients typically do not, despite normal activation in other areas (D. R. Weinberger, Berman, & Zec, 1986). Figure 14.9 shows a normal brain practically lighting up during the

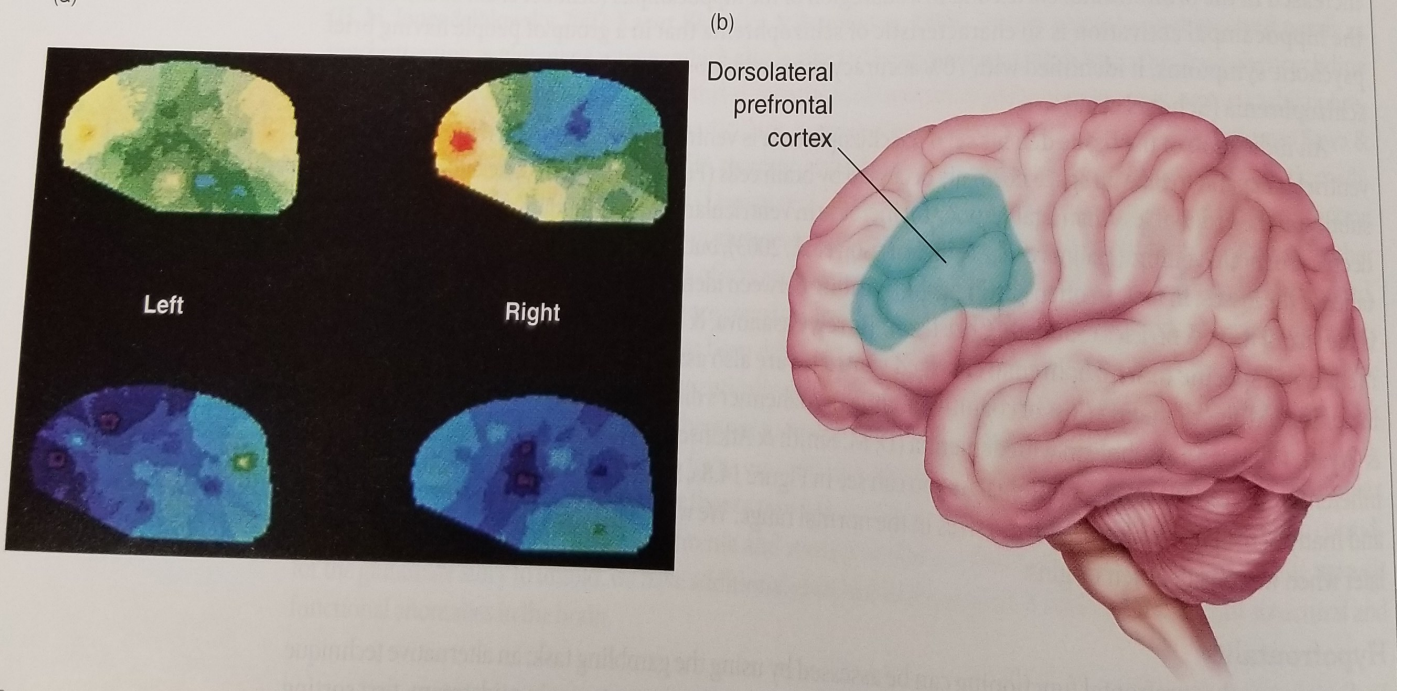
test, in comparison with the schizophrenic brain, especially in the frontal area called the *dorsolateral prefrontal cortex*. This *hypofrontality* apparently involves prefrontal dopamine *deficiency*, because administering amphetamine increases blood flow in the prefrontal cortex and improves performance on the Wisconsin Card Sorting Test (Daniel et al., 1991). Traumatic injury to the dorsolateral prefrontal cortex causes impairments like the symptoms of schizophrenia: flat affect, social withdrawal, reduced intelligence and problem-solving ability, diminished motivation and work capacity, and impaired attention and concentration (Weinberger et al., 1986). Because of the frontal lobes' involvement in planning actions, recognizing the consequences of actions, and managing working memory, it is not surprising that frontal dysfunction would cause major abnormalities in thinking and behavior.

Neural Connections and Synchrony

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

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

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



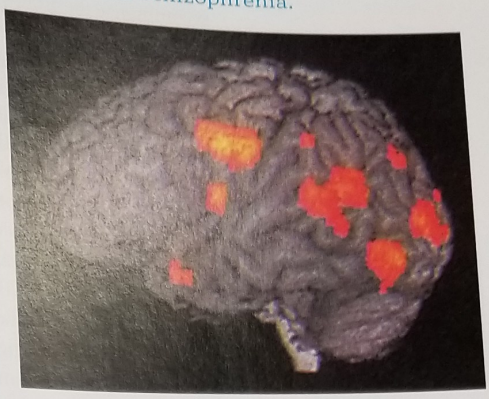
Source: (a) From "Physiologic Dysfunction of Dorsolateral Prefrontal Cortex in Schizophrenia: I. Regional Cerebral Blood Flow Evidence," by D. R. Weinberger, K. F. Berman, and R. R. Zec, 1986, *Archives of General Psychiatry, 43*, pp. 114–124.

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

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

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

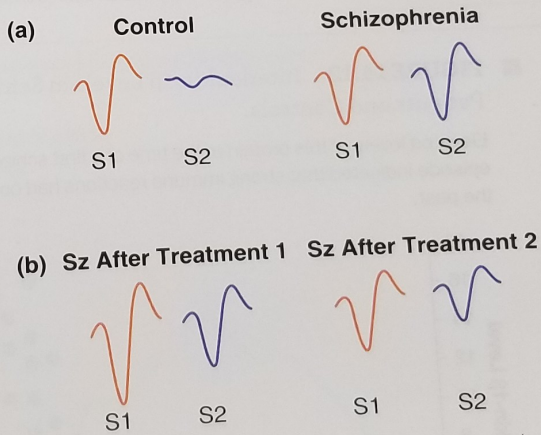
FIGURE 14.10 Brain Activation During Visual and Auditory Hallucinations in a Patient With Schizophrenia.



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

FIGURE 14.11 Absence of P50 Gating in Schizophrenia.

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



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

There may very well be other changes to the brain due to schizophrenia. A large coalition of European researchers and pharmaceutical companies is undertaking a €16.5 million ($18.8 million) study called PRISM (Psychiatric Ratings Using Intermediate Stratified Markers); they will follow individuals with schizophrenia and other neurological disorders to determine the biological roots of the negative symptom of social withdrawal that is common to the groups (Underwood, 2016).

Environmental Origins of the Brain and Transmitter Anomalies

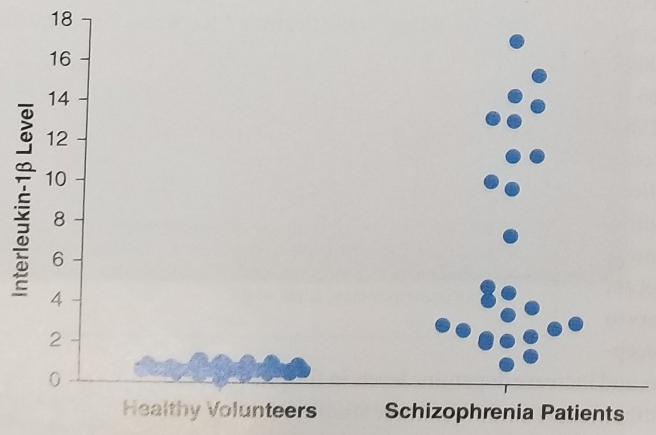
An obvious potential cause of brain defects would be head injury. Several studies have reported an association between schizophrenia and brain damage that occurred within a few years prior to diagnosis (reviewed in David & Prince, 2005). However, the studies have been criticized for several methodological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

The evidence is stronger for a variety of influences at the time of birth or during the prenatal period. These include both physical complications (Cannon, Jones, & Murray, 2002) and emotional stresses on the mother, such as death of the father (Huttunen, 1989) and military invasion (van Os & Selten, 1998). Prenatal stress in mice results in upregulation of 5-HT_{2A} receptors and downregulation of $mGlu_2$ receptors, both of which are seen in the brains of schizophrenia patients (Holloway et al., 2013). One indication that birth and pregnancy complications contribute to brain deficits is that they are associated with enlarged ventricles later in life (Pearlson et al., 1989). They are a possible explanation for the difference in ventricle size between identical twins (Bracha, Torrey, Gottesman, Bigelow, & Cunniff, 1992).

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

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

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



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

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

Several illnesses have been implicated, but the effect of influenza has been researched most frequently, and a higher incidence of schizophrenic births has been confirmed following influenza outbreaks in several countries.

ure 14.13 shows that during years of high influenza infection the birth rate of people later diagnosed with chizophrenia increases during winter and spring; also, there is a peak of such births a few months after the ak of epidemics. However, these studies could not confirm that the individual mothers had been exposed the influenza virus; by analyzing the blood specimens drawn from expectant mothers, Alan Brown and colleagues (2004) found a sevenfold increased risk for schizophrenia and spectrum disorders when influ- antibodies were present, and they estimated that influenza infection accounts for 14% of schizophrenia ses. As was the case with stress, maternal infection with the influenza virus upregulates 5-HT_{2A} receptors d downregulates $mGlu_2$ receptors in the frontal cortex of the offspring (Moreno et al., 2011). Injecting preg- mice with a drug that activates the immune system produced the same result, suggesting that immune sponses are responsible for the receptor alterations in schizophrenia (Holloway et al., 2013).

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

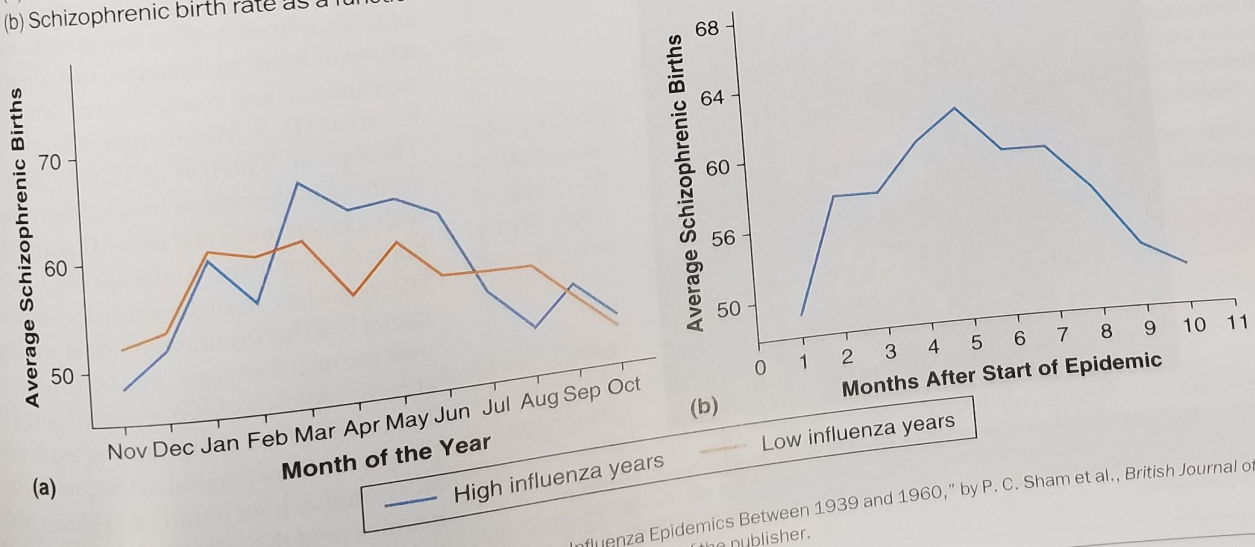
Most of the environmental influences we have been discussing occur during pregnancy or birth; ne, however, relates to the father. There is a greater risk of schizophrenia if the father's age at the time of conception exceeds 25, and by paternal age of 50 the risk has increased by two thirds (B. Miller et al., 2010). The mechanism for this effect is unknown, but chances are it is epigenetic, due either to the nor- al aging process or to an accumulation of external environmental insults. Epigenetic effects in general can e traced to a variety of environmental influences, including toxins, diet, starvation, drugs, and stress; they kely account for most of the environmental influences we have been talking about. The fact that obesity in he Dutch hunger winter offspring was linked to epigenetic changes (see Chapter 6) makes us suspect the ame mechanism in the cases of schizophrenia in that group. This is a relatively new area of investigation, so here has been little documentation of epigenetic influences in schizophrenia.

Schizophrenia as a Developmental Disease

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

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

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



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

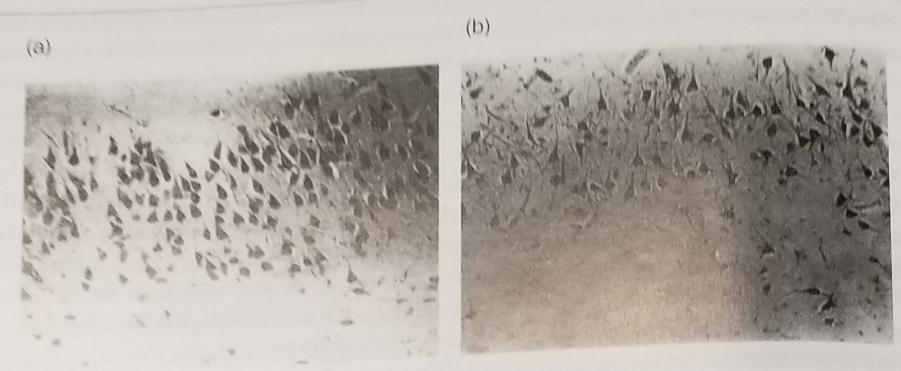


FIGURE 14.14 Neural Disorganization in Schizophrenia.

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

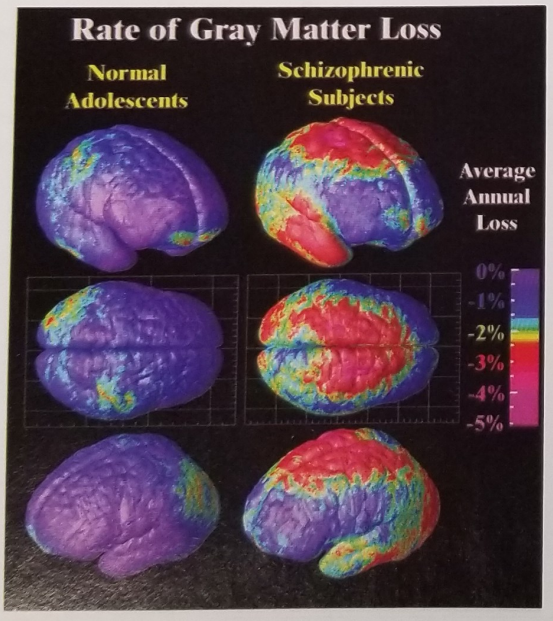
Source: © Arne Scheibel, UCLA.

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

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

FIGURE 14.15 Gray Matter Loss in Schizophrenic Adolescents.

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



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

Gray matter deficit and ventricular enlargement are ordinarily present at the time of patients' diagnosis (Degreef et al., 1992). Most of the evidence indicates that the loss of brain volume occurs rapidly and dramatically in adolescence or young adulthood and then levels off (B. T. Woods, 1998). Adolescence is a particularly significant period in the development of schizophrenia. This is a time when symptoms of schizophrenia often begin to develop and a time of brain maturation, including frontal myelination and connection of temporal limbic areas (D. R. Weinberger & Lipska, 1995). Thompson, Vidal, et al. (2001) identified a group of adolescents who had been diagnosed with schizophrenia and used MRIs to track their brain development. At the age of 13, there was little departure from the normal amount of gray matter loss that occurs with circuit pruning, but over the next five years, loss occurred in some areas as rapidly as 5% per year (Figure 14.15). The nature of the symptoms varied as the loss progressed from parietal to temporal to frontal areas. Studies have found no evidence of dying neurons or of the inflammation that would be expected with an ongoing degenerative disease; instead, gray matter deficits have been attributed to loss of synapses (Jarskog, Glantz,