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Chapter 9

Schizophrenia

LEARNING OBJECTIVES

AFTER READING THIS CHAPTER, STUDENTS WILL BE ABLE TO:

1. Explain why schizophrenia is viewed as one of the most serious, disabling, and complex mental disorders.
2. Identify the steps involved in a DSM-5 diagnosis of schizophrenia and the strengths and weaknesses of this approach.
3. Explain why the concept of diathesis, or vulnerability, is so important in theories of schizophrenia.
4. Describe reasons why genes influence but do not determine who develops schizophrenia.
5. Identify the most common cognitive and neurobiological abnormalities associated with schizophrenia.
6. Identify and explain the contributions of antipsychotic medication and psychosocial therapies to the treatment of schizophrenia.

To understand schizophrenia and why it is arguably the most severe and disabling form of mental disorder, try to suspend, at least temporarily, the compelling images, beliefs, and assumptions that tend to crowd in whenever the word *schizophrenia* is mentioned. Concentrate instead on the words of a patient named Ruth as she describes her experience with the disorder:

> *Around my neck, and hanging down from each shoulder there is something like a creature. It comes at night. I know it's there because I can feel weight. It coils around me yet remains invisible. An invisible burden. It feels like an enormous leech on my body and it touches me in familiar ways and in intimate places. It reeks of animal smells. It has a strong smell that rises from its sliding body. It is incredibly powerful and irresistible. I can't resist it (Heinrichs, 2001, p. 3).*

This woman's name is not really Ruth, but she is a real person and the words are her own, drawn from interview and case notes. Imagine what it must be like to feel and smell something alien and disturbing like this creature and to feel that it has power over you. For Ruth it was not a symptom of an illness, it was an utterly convincing experience. It was her "reality." In fact, the experience was so unpleasant that she thought about suicide as a way of freeing herself. However, she went instead to a local hospital and told the nurses that she was thinking about death. This led to an admission of several weeks during which she was treated for depression—not schizophrenia (see Chapter 8). Ruth never actually told anyone about the creature and only described her thoughts of wanting to die. The antidepressant medication she was given helped with the death feelings, but did not make the "creature" go away. She was eventually given the diagnosis of schizophrenia after describing the creature, reluctantly, to a psychiatrist.

What could do this to a person? Is such a severe mental illness rooted in Ruth's psychological development and background? Unfortunately, the roots of schizophrenia are difficult to find and trace. Ruth was born in an average-size Canadian city, with parents who also seemed to be average in many ways. There is no record of emotional, physical, or sexual abuse in her past, and neither parent was ever treated for psychiatric problems. Ruth had average marks until the second year of high school, when concentration problems began to emerge. Her marks slipped badly and she stopped doing homework. About this time she suddenly decided to drop out of school and marry her boyfriend. But the marriage lasted only a few months because her new husband left and refused to return. A short time later Ruth began to think about death, and it is unclear exactly when the "creature" experience began.

Did rejection cause her disorder? It certainly didn't help, but if emotional pain and rejection were sufficient to cause insanity, wouldn't we all become insane at some time in our lives? In any case, Ruth is just one person with schizophrenia and the disorder has many forms and faces. Consider William, for example, as he describes his experience of schizophrenia:

> *The most hilarious aspect of the hospital is the shower. Why would they ask God to have a shower? This makes me laugh. I have heard the voices of great men in history and seen the rainbow of hope. I am willing to take on da Vinci and beat him, but the rhythm of the building is hypnotic and it unbalances me. If only they would do EEG and IQ tests I could prove that I am God. My beard has grown to fulfill the prophecy of a King of Kings, and I know that my powers will be lost on my 33rd birthday. I anticipate my crucifixion. But I will search for the devil and kill him. Perhaps if I kill my brother I will be the only son in the Father's eye. Yes, I must go and look for my brother the devil (Heinrichs, 2001, p. 4).*

Unlike Ruth's situation and voluntary admission, it was the police who often brought William to hospital. For example, on one occasion the landlord went to William's apartment looking for unpaid rent. The door was wide open and William was running around the rooms smearing excrement on the walls and furniture. On other occasions he became involved with street drugs and alcohol and was charged with assault. Moreover, a look into William's life and background shows that his mother had schizophrenia and attempted suicide. His father seems to have had normal physical and mental health. William's problems began early with learning difficulties and failures in primary school grades. He left after one year of high school and tried to work, but soon drifted into gang organizations and the use of street drugs and spent a year in jail. Indeed, until his mid-twenties he was more likely to be known to police and spend time incarcerated than to have contact with mental health professionals or hospitals. William subsequently had many psychiatric hospital admissions and was extensively assessed and examined. For example, it was found that he had abnormal reflexes even though his brain scan was normal. In addition, his electroencephalogram (EEG) suggested the possibility of a seizure disorder (epilepsy). Nonetheless, his diagnosis was schizophrenia.

Ruth and William are two very different people who share the same diagnosis. Ruth's family background is largely empty of clues about the causes of mental illness, although she did experience a severe and painful personal rejection. William, in contrast, grew up with familial mental illness and experienced many adjustment difficulties and social adversity long before his psychotic symptoms emerged. He also showed "soft" signs of brain damage. There is no shortage of potential clues in William's case. The two patients with schizophrenia also differed in their symptoms. Ruth was convinced that she could smell and feel a "creature," whereas William tried to live out his "divinity" and "heard" and "spoke" with famous historical figures. Ruth felt weak and controlled and William felt strong and powerful. How can patients be so different and still have the same disorder?

(Based on information presented in Heinrichs, 2001.)

Introduction and Historical Perspective

Across the range of abnormal psychology and psychiatry, is there a disorder as strange and challenging, as poorly portrayed and misunderstood as **schizophrenia**? It is difficult to read about this severe form of mental disorder with an open mind and difficult to resist the popular assumptions and widely held beliefs that spring up whenever the puzzling disorder is mentioned. Images of "raving lunatics," so-called crazy people with danger if not murder in mind, people who are completely irrational and unpredictable—these are the associations of the word *schizophrenia*. And then there is the incorrect idea that the disorder involves a "split personality," people within people, perhaps in conflict or completely unaware of each other. Of course, not all preconceptions about schizophrenia are negative and sinister. There is also the notion that a person with the disorder is unusually creative or "spiritual," perhaps misunderstood and alienated, but with special insights into the meaning of life and with special access to sources of inspiration and genius denied to "normal" people. Most of these assumptions and ideas are inaccurate or at most partly true. This chapter will explore what is known about schizophrenia—its characteristic features, possible causes, and current treatments.

The two case studies of Ruth and William illustrate an important and basic fact about the disorder: schizophrenia is a complex condition characterized by **heterogeneity**. In other words, there is a tendency for people with the disorder to differ from each other in symptoms, family and personal background, response to treatment, and ability to live outside of hospital. Heterogeneity makes it difficult to predict how a person will be affected by schizophrenia; what their prospects are for the future; and whether their condition will improve, stabilize, or worsen. For example, a significant proportion of patients,

perhaps more than 50 percent, improve over time and in response to treatment (Buchanan & Carpenter, 2000; Möller & Von Zerssen, 1995). Indeed, although there is no cure, the outlook for a person with schizophrenia is better than ever before in terms of treatment options and both drug and psychological therapies. Yet not all patients benefit from medication. For example, up to one-third of patients continue to suffer from positive symptoms like hallucinations or delusions (Tandon, Nasrallah, & Keshavan, 2010), some endure unpleasant side effects, and many are difficult to assist with counselling or rehabilitation. Also, what does "getting better" really mean? Does it mean that symptoms disappear, or should it also mean that a person is able to resume his or her career and educational plans, reconnect with friends and family, and lead a normal life (Shrivastava, Johnston, Shah, & Burueau, 2010)? Which patients will do relatively well, and which will struggle with partly controlled symptoms and persisting distress for most of their lives? There are no clear answers to these questions. Moreover, many patients and their families have to cope with the stigma and negative image associated with serious mental illness (Corrigan, 2004). Hence, it is not surprising that a sense of pessimism and uncertainty still surrounds schizophrenia.

PREVALENCE, ONSET, DEMOGRAPHIC AND SOCIO-ECONOMIC FEATURES

In North America and Europe there is about a 1 percent risk that a person will develop schizophrenia at some point in his or her life. However, the **prevalence**, or total number of cases with the disorder at a given point in time, changes depending on how the diagnosis is made (Government of Canada, 2006; Mueser & McGurk, 2004). If the estimated prevalence rate of 1 percent is accepted, schizophrenia is twice as common as Alzheimer's disease and five times as common as multiple sclerosis. Hence, there may be more than 300 000 people with schizophrenia in Canada.

The development of psychotic or positive symptoms marks the formal onset of the first episode of schizophrenia. While it is possible for the disorder to develop at any age, positive symptoms tend to manifest between late adolescence and early adulthood (typically between 15 to 45 years of age). The onset of schizophrenia may be abrupt or gradual, but most often a variety of clinically significant symptoms emerge slowly over time. Men and women are at equal risk, but the disorder seems to strike men several years earlier (Häfner & an der Heiden, 1999; Norquist & Narrow, 2000). Specifically, the first psychotic episode tends to occur in the early to mid 20s for males and in the late 20s for females (American Psychiatric Association [APA], 2013). Schizophrenia rarely occurs before adolescence or after 45 years of age. If the disorder develops after the age of 45, it is more common among women and seems to comprise more emotional and mood-related symptoms (Government of Canada, 2006).

Predicting the course and outcome of schizophrenia in individual patients is difficult and in need of further investigation. Overall, poor outcome is more likely among males, individuals who develop the disorder at a younger age, and those who experience a longer delay between the first appearance of symptoms and treatment (Häfner & an der Heiden, 1999). While the course of schizophrenia varies substantially across individuals, it tends to be a chronic and relapsing disorder. The course appears to be favourable in approximately 20 percent, with approximately 1 in 7 patients experiencing recovery (APA, 2013; Jääskeläinen et al., 2012).

Schizophrenia occurs throughout the world, but more frequently in lower socio-economic groups (Bresnahan & Susser, 2003). Once individuals have developed the disorder, they are less likely to complete their education or to find and maintain employment (Müijen & Hadley, 1995). They are more likely to develop additional psychiatric problems, including depression and suicide attempts as well as drug and alcohol abuse (Kendler, Gallagher, Abelson, & Kessler, 1996). These experiences are part of the social drift that affects many patients (Johnson, Cohen, Dohrenwend, Link, & Brook, 1999). And then there are the financial and social costs associated with this disabling and often lifelong condition. According to the Canadian Mental Health Association, schizophrenia rivals stroke and heart disease in terms of hospital care, with 1 out of 12 beds occupied by people with the disorder. In addition, costs to the Canadian taxpayer total approximately $6.85 billion annually in direct and indirect health care, family benefits, social support services, and productivity loss due to morbidity or early mortality (Goeree et al., 2005). More global measures estimate that approximately 3 percent of the total burden of human disease is attributed to schizophrenia. By any measure schizophrenia places a heavy burden on patients, their families, and society.

Over the last three decades, with the rapid growth of knowledge about brain biology and genetics, research on schizophrenia has increased substantially. The number of articles published on the disorder has multiplied since the early 1970s to the current rate of almost 5000 articles a year. Similarly, the International Congress on Schizophrenia Research attracted only 175 attendees when it met for the first time in 1987. By 2011 attendance had grown to more than 1100 researchers, clinicians, and students from over 45 countries and the conference included over 1000 scientific presentations. In Canada, research funding has increased through the Canadian Institutes of Health Research and provincial granting agencies. The National Institute of Mental Health in the United States is directing enormous resources—billions of dollars—to serious mental illness. Yet, despite these efforts, understanding schizophrenia remains a major

FOCUS 9.1

An Eighteenth-Century Sculptor with Schizophrenia

Although at least one review (Hare, 1988) has concluded that no clear examples of schizophrenia-like illness can be found in the eighteenth century, one probable case is well known to historians of European art. Franz Messerschmidt (1736–1783) was born and studied in Munich, Germany, and then found employment at the imperial Austrian court in Vienna. There is no doubt that he was an artist of major talent and many contemporaries recognized his outstanding skills as a sculptor and portraitist (see Pötzl-Malikova, 1982). Yet signs of mental disorder were noted soon after he received a teaching appointment in 1769. Although never described as "insane," he was passed over for promotion because of persisting reports of "confusion" and a "not perfectly healthy imagination." Messerschmidt complained that all other teachers were his enemies and he fled from Vienna, eventually living for many years alone on the outskirts of Bratislava.

It seems clear that Messerschmidt had psychological problems, but did he suffer from schizophrenia? There is no evidence that he was ever hospitalized for insanity, although he may have consulted physicians, including, perhaps, Franz Mesmer, the father of hypnosis (see Pötzl-Malikova, 1987). However, it is possible to make a good case for the disorder even in the absence of hospital or physician records. The evidence takes the form of a visitor's account of Messerschmidt's conversations, living situation, and artistic production, written by Friedrich Nicolai in 1785. Nicolai was a travel writer and apparently gained the sculptor's trust to the point where Messerschmidt was willing to talk about his artwork and creative process. Of special interest from the standpoint of abnormal psychology were the artist's descriptions of nightly visits by demons. These demons tortured him "despite having lived a life of chastity." One demon in particular was troublesome, and was referred to as the "demon of proportion." This demon was envious because the artist had almost achieved perfect proportion in his sculpture. Part of the demon's torture involved causing Messerschmidt pain in his lower abdomen and thighs, especially when he was sculpting a part of the face that "is analogous to a certain part of the lower region of the body." In order to control such demons Messerschmidt pinched himself in the right side under the ribs and simultaneously grimaced into a mirror "in the exact required relationship to the pinching of his flesh." According to Nicolai, the sculptor worked on his piece, looked into the mirror at half-minute intervals, and made "with the greatest exactitude, precisely that grimace which he just needed." An example of one of these sculptures is presented in the photograph.

Franz Xaver Messerschmidt (1736–1783), *Der Gähner* (*The Yawner*). During the years of his illness, Messerschmidt sculpted a series of portrait heads that were given fanciful names after the artist's death. However, it is likely that many were self-portraits and expressed his experience of being tormented by psychotic delusions. Reproduced with permission of the Szépmüvészeti Múzeum, Budapest.

Messerschmidt's experience of being persecuted by envious demons who could be controlled by sculpted facial expressions may represent the kind of **delusional thinking** seen frequently in schizophrenia. In addition, his career decline, increased social isolation, and withdrawal are typical consequences of the modern disorder. Although the biography of Messerschmidt is incomplete, the information on his life and disorder are highly suggestive of a schizophrenia-like condition. And this from a century declared devoid of medical and psychiatric accounts of the condition.

scientific challenge. It is not even known if the disorder has been part of the human condition for thousands of years or whether it is a latecomer, a "new" disorder that was rare before the year 1800. Could it be that schizophrenia is a "modern" condition and only about 200 years old (see Focus box 9.1)?

1 BEFORE MOVING ON

Why is schizophrenia regarded as so disabling and in need of so much research funding and support?

HISTORICAL PERSPECTIVE: THE MISSING ILLNESS

It is often assumed that schizophrenia-like illness has always existed because "**madness**" and "insanity" have been documented since the beginnings of civilization, medicine, and writing. Certainly, there are many examples of irrational and bizarre behaviour in the Bible, in other ancient texts, and in the writing of many non-Western cultures (Haldipur, 1984; Hershkowitz, 1998; Jeste, del Carmen, Lohr, & Wyatt, 1985). Yet it is a mistake to assume that a disorder akin to modern schizophrenia

has always been part of the human condition. In other words, although "madness" in some form existed in the past, it is uncertain whether these historical disturbances included schizophrenia. For example, descriptions of madness and "**lunacy**" before about 1800 suggest that these conditions occurred at any time of life rather than primarily in young people. In addition, experiences like **auditory hallucinations** or "hearing voices" and other sounds occur in up to 70 percent of patients with schizophrenia at some point during their disorder (Andreasen & Flaum, 1991). Yet auditory hallucinations are extremely rare in cases of madness prior to 1700 (Hare, 1988; Torrey & Miller, 2001). Moreover, historically documented madness seldom lasted more than a few days, and was often drug and alcohol–induced or related to other diseases. In fact, the first recognizable descriptions of modern schizophrenia did not appear in English or French until the early years of the nineteenth century (Haslam, 1809/1976; Pinel, 1809).

The historical evidence and lack of case material have encouraged the view that a schizophrenia-like disorder was very rare, perhaps even absent, until the late eighteenth century. Then, for some reason, cases of insanity surged, with physicians and asylum custodians unable to cope with the rapid increase in numbers. For example, careful record keeping in Canada's Maritime provinces shows that the number of insanity cases per 1000 people in the population increased by more than 2000 percent between 1847 and 1960 (Torrey & Miller, 2001)! It has been speculated that increasing industrialization, the movement of people to cities from towns and countryside, and environmental changes may have been involved in the sudden and escalating emergence of schizophrenia in modern life.

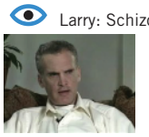
Of course, the idea that schizophrenia is a recent disorder has many critics. Turner (1992) argued that people in earlier times viewed mental disorder differently and may not have recorded or commented on symptoms and characteristics that help to separate schizophrenia from more generic categories like "lunacy" and insanity. Thus, the disorder existed but was not recognized as a distinct entity until Haslam's (1809/1976) case studies and the later and definitive descriptions of Kraepelin (1896, 1919) and Bleuler (1911/1950). It is important to note, however, that some "modern" psychiatric disorders, including mania and depression (Porter, 1995) as well as mental retardation (Berrios, 1995), are recognizable in historical medical texts and even in ancient writings. Accordingly, there is no easy answer to the question of whether schizophrenia existed in the distant past, and the historical origins of the disorder are likely to remain controversial and uncertain (Heinrichs, 2003).

Typical Characteristics

POSITIVE (PSYCHOTIC) AND NEGATIVE SYMPTOMS

Characteristic symptoms of schizophrenia may be broadly classified as either positive or negative. **Positive symptoms** refer to exaggerated, distorted adaptations of normal behaviour. They include the more obvious signs of **psychosis**, namely, delusions, hallucinations, **thought and speech disorder**, and grossly disorganized or **catatonic behaviour**. **Negative symptoms**, on the other hand, refer to the absence or loss of typical behaviours and experiences. Negative symptoms may take the form of sparse speech and language, social withdrawal, and **avolition** (apathy and loss of motivation). **Anhedonia** (an inability to feel pleasure, as well as lack of emotional responsiveness) and diminished attention and concentration are also considered negative symptoms.

Larry: Schizophrenia



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HALLUCINATIONS **Hallucinations** are misinterpretations of sensory perceptions that occur while a person is awake and conscious and in the absence of corresponding external stimuli. In other words, people hear, see, smell, or feel things that are not really present. Alternatively, perhaps they misinterpret normal sensory experiences. Hallucinations occur in all sensory modalities, but auditory hallucinations, in which the person hears voices or noises, are the most common form experienced by patients with schizophrenia. These voices are perceived as distinct from the patient's own thoughts and may include instructions to perform actions that involve self-harm or danger. They may urge the patient to stop fulfilling his or her responsibilities, or the voices may be insulting at one point and complimentary at another. Emil Kraepelin (1919), who first described schizophrenia in detail, mentioned patients who "heard" the roars of Satan, but also whispering children and laughter. One man was told where to stand and when to smile, whereas another heard gossip about his own behaviour.

Research suggests that hallucinations may develop from a "misattribution of sensory experience." This involves an inability to discriminate between internal and external sources of information and experience. Findings by Laroi and Woodward (2007) reveal that patients with schizophrenia who have hallucinations confuse their own responses and the responses of other people. Hence, Ruth, the patient who smelled and felt a creature around her neck, may have failed to recognize her own body and instead experienced its sensations as stemming from somewhere—or something—else. Similarly, hearing voices may result from patients' inability to recognize their own thoughts and a tendency to attribute them to external sources.

DELUSIONS **Delusions** are implausible beliefs that persist despite reliable contradictory evidence. They reflect a disorder of thought content and may include a complex delusional belief "system" or just a single belief relating to one aspect of daily life. Delusions may reflect persecutory, referential, somatic, religious, or grandiose themes and meanings (see Table 9.1). **Persecutory delusions**, or "paranoid" delusions, in which individuals believe that they are being

TABLE 9.1 COMMON DELUSIONS EXPERIENCED BY PATIENTS WITH SCHIZOPHRENIA

Type	Content	Examples
Persecutory	A belief that the individual is being conspired against, deceived, or persecuted	"Strangers on the street are undercover agents following me."
Referential	A belief that events, objects, or other individuals have personally relevant meaning	"Each song that a DJ selects for a radio playlist represents a special truth about my life."
Somatic	Perception of a change or disturbance in personal appearance or bodily function	"My body is inhabited by extraterrestrial beings that give me headaches."
Religious	Unusual religious experiences or beliefs	"Satan is leaving messages for me in television programs and emails."
Grandiose	Possession of special or divine powers, abilities, or knowledge	"I have the power to change the course of history."

pursued or targeted for sabotage, ridicule, or deception, are the most common form of delusion. Kraepelin (1919) described patients who were convinced that hospital attendants were poisoning the food and water or that the German emperor's spies were tracking them.

Referential delusions involve the belief that common, meaningless occurrences have significant and personal relevance. The advertisement on the back page of a magazine, for example, may be interpreted as a signal to eat a specific cereal for breakfast. In contrast, **somatic delusions** involve beliefs related to the patient's body. Kraepelin (1919) described patients who were convinced that their inner organs had been turned to dust or that they had a special "nerve" of laughter in their stomachs that was the origin of all humour in the world.

A **religious delusion** often involves the belief that biblical or other religious passages or stories offer the way to destroy or to save the world. The case of William, described at the beginning of the chapter, illustrates how someone can believe that he is living out a biblical prophecy. Similarly, **delusions of grandeur** may entail a belief in divine or special powers that can change the course of history or provide a communication channel to God. For example, Kraepelin (1919) described a patient who believed that all the world's armies were under his personal command.

One theory proposes that persecutory delusions develop in people who make interpretations of experience too quickly and jump to conclusions based on minimal evidence (Freeman, Pugh, & Garety, 2008; Garety & Freeman, 1999). Another theory proposes the existence of a bias in reasoning so that negative events are always perceived as coming from the environment or from other people (Bentall, 1994). Still another theory holds that persecutory delusions reflect an inability to imagine the feelings, perspectives, and experiences of other people (Corcoran, Cahill, & Frith, 1997).

DISORGANIZED SPEECH AND THOUGHT DISORDER

Unusual-sounding, nonsensical speech often signifies the existence of a formal thought disorder, a characteristic given great emphasis by the pioneering Swiss psychiatrist Bleuler (1911/1950) in his early descriptions of schizophrenia. The disorganization of speech in patients with schizophrenia presents itself in several ways. **Loosening of associations** and logical connections between ideas occurs and the thought-disordered patient shifts quickly from one topic to another. In addition, answers to questions are "tangential" or hardly related to the original point or request being made. Bleuler gave many examples of this kind of disturbance, including one by a patient who wrote a letter explaining the nature of the Catholic rosary as "a prayer multiplier, and this in turn is a prayer for multiplying and as such is nothing else but a prayer mill, and is therefore a mill-prayer machine which is again a prayer-mill machine" and continued in this way for several pages (Bleuler, 1911/1950, pp. 19, 28). In current practice, a common way to elicit thought and language disorder is to ask a patient to explain a proverb or saying. For example, one man explained the proverb "Don't change horses when crossing a stream" in the following way: "That's wishbell. Double vision. It's like walking across a person's eye and reflecting the personality. It works on you, like dying and going to the spiritual world, but landing in the Vella world" (Harrow, Lanin-Kettering, & Miller, 1989, p. 609). Thought disorder reveals itself in the structure of spoken or written language and therefore provides a more objective index of schizophrenic disturbance than symptoms like hallucinations and delusions. However, it is the least common of the positive symptoms (Andreasen & Flaum, 1991).

Thought disorder may reflect the presence of more basic cognitive problems in symptomatic patients. A reduction in the amount of information a person can hold in immediate memory at one time, distractibility, unawareness of language deviations, and inconsistencies and abnormal "spread" of activated word meanings all seem to associate with this symptom (Kreher, Holcomb, Goff, & Kuperberg, 2008; Kuperberg, McGuire, & David, 1998).

NEGATIVE AND EMOTIONAL SYMPTOMS

In contrast to the reality distortion of positive symptoms, the negative symptoms of schizophrenia represent deficits and losses in normal functioning. They include avolition and restricted affect. Avolition, or apathy, refers to the inability to initiate and persevere in activities. In addition, many patients have **affective flattening**—a lack of emotional expressiveness, failing to convey any feeling in their face, tone of voice, or body language. The range and intensity of emotional expressiveness is often restricted in schizophrenia. Anhedonia is consistent with the patient's apathy and denotes a lack

of pleasure or reward experiences. Negative symptoms of schizophrenia may also be seen in the deterioration of academic or occupational proficiency that is usually observed, perhaps due to a weakening in cognitive efficiency.

Bleuler (1911/1950) was especially impressed with the apparent lack of emotional response in many patients with schizophrenia when crisis situations or emergencies were encountered. For example, he described an emergency evacuation prompted by fire on the hospital ward and noted a striking lack of interest and concern in several patients. Many also neglected their appearance and seemed to lack any drive or motivation, spending long hours in silent and solitary detachment from other people. Negative symptoms are moderately associated with impairment on objective tests of cognitive abilities, including attention, learning and memory, and mental efficiency, and also relate to everyday functioning and community adjustment (Green, 2001; Harvey, Koren, Reichenberg, & Bowie, 2006).

MOTOR SYMPTOMS AND GROSSLY DISORGANIZED OR CATATONIC BEHAVIOUR These behaviours refer to deficits in motor function ranging from agitation to immobility. Grossly disorganized behaviour also reflects difficulty with goal-directed behaviour. It thus often manifests itself in unpredictable movements; problems performing everyday activities, such as dressing or preserving personal hygiene; and inappropriate sexual behaviour. Catatonic behaviour, in contrast, refers to the other end of the motor spectrum. It involves a significant reduction in responsiveness to the environment wherein patients assume unusual and rigid postures and resist efforts by others to change their position. Alternatively, they may engage in random, undue motor activity, or exhibit **waxy flexibility**, allowing others to move their body and limbs and then maintaining the new position. Catatonic behaviour, especially the rigid maintenance of postures and positions, seems to have been common in the time of Kraepelin (1919) and Bleuler (1911/1950) and is now observed less frequently (Andreasen & Flaum, 1991). However, agitated and disorganized movements and extreme unresponsiveness to the environment are still seen in some patients.

Diagnosis and Assessment

DSM-5 DIAGNOSTIC CRITERIA

The diagnosis of schizophrenia is based on six diagnostic criteria identified by the DSM-5 (APA, 2013; see Table 9.2). These criteria encompass a combination of symptoms and clinical features that are considered to define the disorder. They include characteristic symptoms (Criterion A), marked social or occupational dysfunction during the course of the disorder (Criterion B), persistence of the disturbance for at least six months (Criterion C), the exclusion of concurrent schizoaffective or mood disorders during the active phase of schizophrenia symptoms (Criterion D), the exclusion of substance use or medical conditions as a causal influence of the disorder (Criterion E), and consideration of any history of autism spectrum disorder or a communication disorder of childhood onset (Criterion F). The characteristic symptoms of schizophrenia include delusions (Criterion A1), hallucinations (Criterion A2), disorganized speech (Criterion A3), grossly disorganized or catatonic behaviour (Criterion A4), and negative symptoms

TABLE 9.2 DSM-5 DIAGNOSTIC 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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FOCUS 9.2

Schizophrenia: Fact and Fiction

Schizophrenia is a complicated disorder surrounded by false beliefs and half-truths. For example, the disorder has nothing to do with "split" or multiple personalities, but this incorrect idea persists in the public mind and entertainment media. Another inaccuracy involves a perceived connection to violence. Many people seem to think that a mental disorder necessarily makes people dangerous and aggressive. However, research shows that schizophrenia associates with only a slight, statistically significant increase in the risk of violent behaviour (Douglas, Guy, & Hart, 2009; Walsh, Buchanan, & Fahy, 2002). Aggression is most common among younger male patients with a history of violence, a tendency to stop taking medication, impulsivity, and substance abuse (APA, 2013). In fact, drug abuse rather than mental illness by itself seems to substantially increase the risk of violent behaviour (Fazel, Gulati, Linsell, Geddes, & Grann, 2009). The vast majority of people with schizophrenia are not violent and are more likely to be victims of crime than is the general public (Brekke, Prindle, Bae, & Long, 2001).

Instead of aggression against others, schizophrenia brings with it a greater risk for self-harm in the form of suicide (Palmer, Pankratz, & Bostwick, 2005). Approximately 20 percent of individuals with the disorder attempt suicide on one or more occasions and 5 percent succeed (Hor & Taylor, 2010). Suicidal behaviour may be a response to the depressive mood experienced by many patients, but may also reflect the influence of delusions and hallucinations (Hor & Taylor, 2010). Recall the case of Ruth described in the beginning of the chapter. She viewed the idea of taking her own life as a way to escape from very upsetting symptoms.

Another widely held belief is that people with schizophrenia cannot lead productive lives and invariably end up as homeless "street people." This is certainly not true. Many people with the disorder can work, live independently, and contribute to society. However, deficits in cognition, including social cognition, the stigma of mental illness, and lack of support make it difficult for patients to live autonomously, finish their education, maintain employment, and establish friendships and romantic relationships (Bowie et al., 2008; Penn, Sanna, & Roberts, 2008). Nonetheless, many patients with schizophrenia do well living in the community if they receive appropriate treatment and support.

An unfortunate fact about the disorder is that it significantly increases the likelihood of substance abuse involving alcohol, cannabis (marijuana), and nicotine. It is remarkable that people with schizophrenia seem especially prone to nicotine addiction, with over half smoking cigarettes on a regular basis (APA, 2013). Indeed, smoking is more common in schizophrenia than in other psychiatric disorders, with rates up to 90 percent reported in some studies (de Leon & Diaz, 2005; Strand & Nybäck, 2004; Ücok, Polat, Bozkurt, & Meteris, 2004). Furthermore, people with schizophrenia find it extremely hard to quit smoking and tend to start again after completing programs designed to help them stop (Evins et al., 2007).

The reason why smoking rates remain so high in schizophrenia is puzzling, but research is providing clues. Patients with the disorder may smoke to help them cope with the negative symptoms and cognitive deficits they experience (Kumari & Postma, 2005). Unlike other forms of substance use, smoking may have benefits for patients because studies show that nicotine seems to improve cognitive brain functions, including attention, memory, and sensory processing (Dulude, Labelle, & Knott, 2010; Fisher et al., 2012; Harris et al., 2004). It follows that cognitive deficits are most severe in non-smoking patients with schizophrenia (Wing, Bacher, Sacco, & George, 2011). No wonder smoking patients find it hard to quit!

(Criterion A5). The first four symptom-related diagnostic criteria for schizophrenia reflect positive symptoms, comprising the more obvious signs of psychosis. The fifth characteristic symptom encompasses negative symptoms. The DSM-5 recognizes two negative symptoms, namely, avolition and affective flattening.

The DSM-5 definition of schizophrenia has been likened to a diagnostic "menu." In other words, the disorder is not defined by any one symptom or cluster of symptoms. Rather, a selection of qualitatively different symptoms is required for a diagnosis and none are unique to schizophrenia. Criterion A specifies that a minimum of two out of the five characteristic symptoms must be present concurrently during the period of acute disturbance referred to as the "active phase" of the disorder. However, the DSM-5 states that the individual must have at least one of three core positive symptoms: delusions, hallucinations, and disorganized speech for a reliable diagnosis.

CASE EXAMPLES Consider Ruth and William and the way their respective clinical profiles fit into the DSM-5 diagnostic criteria for schizophrenia (APA, 2013). Ruth experienced tactile (touch) and olfactory (smell) hallucinations of an animal, which she believed to be hanging around her neck. At least one more characteristic symptom was required for diagnosis. She exhibited withdrawal and affective flattening, which are negative symptoms of schizophrenia. Ruth thus met Criterion A for schizophrenia. William, on the other hand, experienced bizarre religious and grandiose delusions of divinity as well as auditory hallucinations and displayed grossly disorganized behaviour. His symptom picture actually exceeds the number required by the DSM-5 Criterion A.

Both Ruth and William exhibited deterioration in personal, social, and occupation functioning, thus meeting Criterion B for schizophrenia. Ruth neglected her personal hygiene. As well, she was unable to live successfully in supported housing. William was unable

to live independently, at times vomiting, defecating, and urinating in his apartment, or engaging in chaotic behaviour. Ruth and William also met Criterion C for schizophrenia, each presenting with more than one month of active symptoms, and experiencing the disturbance for over six months.

It is important and sometimes difficult to distinguish the negative symptoms of schizophrenia from depressive and other mood-related symptoms and also to ensure that positive symptoms do not reflect mood-congruent delusions and hence a mood disorder rather than schizophrenia. Ruth's emotional flatness and withdrawal, thoughts of death, suicidal ideas, hopelessness, and self-deprecation suggest the presence of severe depression with psychotic features. However, careful questioning and review of hospital records and interview notes showed that her hallucinations and withdrawal persisted even when mood-related symptoms improved. This led to the conclusion that she met Criterion D for schizophrenia.

Additional "exclusionary" criteria include elimination of drug effects or coexisting diseases as causes of psychosis or negative symptoms (Criterion E), as well as the possibility of developmental and childhood disorders as contributing causes (Criterion F). William's history of street drug abuse was excluded as a cause of his psychotic episodes because the episodes occurred independently of his drug intake. Further, although William's childhood history included schooling problems and poor social adjustment, there was no evidence of autism spectrum disorder or communication disorders. Ruth's history was completely clear of both substance abuse and developmental problems.

CRITIQUE OF DSM-5 AND AREAS FOR FURTHER STUDY

While the DSM-5 diagnosis is currently used as the primary definition of schizophrenia, it is important to be aware of its limitations. The DSM-5 relies on a person's presenting symptoms and history as the main indications of disorder. A significant drawback of this approach to diagnosis is its subjectivity. Symptoms are private experiences that a patient describes to a clinician. There are no instruments that can indicate the presence and intensity of a delusion in the way that a thermometer can indicate a fever. Hence, there is also no independent way to confirm a diagnosis of schizophrenia because the DSM-5 system lacks objective signs or laboratory findings. Although clinicians using structured interviews and explicit diagnostic criteria tend to agree on who has or does not have the disorder, the diagnosis may still be inaccurate. In other words, a reliable diagnosis does not necessarily produce a valid diagnosis. For example, it was once common to hear terms such as *paranoid* (defined by delusions or hallucinations alone) or *catatonic* (defined by abnormal movements or posture) or *undifferentiated* (a mixture of symptoms) schizophrenia applied to the disorder. However, DSM-5 does not recognize or include these distinctions. By themselves symptoms are a poor way of breaking a disorder down into different "kinds" or subtypes even if they seem to make sense. Symptoms often change, and many patients appear to have paranoid schizophrenia at one time only to receive a diagnosis of undifferentiated schizophrenia a year later. Accordingly, symptom-based subtypes have questionable validity and low reliability, and, therefore, also have little value for clinical description and research (Tandon, Narallah, & Keshavan, 2009). Nevertheless, some symptoms used to define subtypes, such as catatonia, are now used as "specifiers" to provide further descriptive detail in diagnosis.

The definition of schizophrenia continues to develop as advances in research, treatment, and diagnostic tools continue to shape its conceptualization. It is important that the boundaries of any disorder are clearly defined and distinct from related conditions. At the same time, some "grey areas" are recognized. Hence, the DSM-5 includes a new condition called *attenuated psychosis syndrome*. This condition, which requires more study, identifies a person who does not yet have a full-blown psychotic disorder, but who does exhibit mild versions of psychotic symptoms. Identifying individuals with a heightened risk for developing a psychotic disorder is required when attempting prevention or early treatment, but further research is required to determine whether or not this new distinction is useful.

2 BEFORE MOVING ON

Why would a person who thinks he hears voices not necessarily receive a diagnosis of schizophrenia?

MARKERS AND ENDOPHENOTYPES FOR SCHIZOPHRENIA

What would be required to verify objectively that a person has a disorder like schizophrenia? Objective diagnosis is possible if measurable **disease markers** can be identified, markers that occur in virtually all people with the illness. In principle, a marker is any physical, psychological, or biological characteristic or trait. For example, Alzheimer's disease involves degenerative changes in nerve cells. These changes are observable under a microscope and represent pathological markers that confirm the disease. While symptoms reflect a disturbance in mind and body that is associated with schizophrenia, they are too subjective and private to confirm a diagnosis of the illness. Markers introduce scientific precision into the diagnostic process.

A disease marker for schizophrenia could be any objective psychological as well as physical sign of the illness or of vulnerability to the disorder. For example, Canadian psychologist Richard Steffy argued that the time required to prepare for and respond to simple perceptual events may be an indicator of severe and chronic forms of schizophrenia (Steffy & Waldman, 1993). More generally, a person who exhibits a marker for schizophrenia either has the

disorder presently or is likely to develop schizophrenia in the future. A true marker for schizophrenia would be very common among patients with the DSM-5 schizophrenia diagnosis. This high prevalence reflects the marker's **sensitivity** to the disorder. At the same time, the marker must occur very infrequently among healthy people or people with other disorders, reflecting the marker's **specificity** for schizophrenia.

It is possible to further subdivide the marker concept into vulnerability and genetic markers, as well as the closely related concept of **endophenotypes**. A vulnerability marker is a stable and enduring sign or trait of the disorder that occurs before a person actually succumbs to the disorder and experiences symptoms. A vulnerability marker reflects an inherent predisposition to develop the disorder. Such a marker thus allows for the identification of people at risk for becoming ill, even though they may be healthy when the marker is first observed. A genetic marker is a special kind of vulnerability marker. Hence, it is stable and enduring, presents long before onset of the illness, *and* occurs in close relatives of the patient, particularly those who develop schizophrenia. Prevalence among family members implies a genetic component to the marker. Genetic and vulnerability markers may define endophenotypes, which are biological or behavioural predispositions that make the disorder more likely. An endophenotype is "intermediate" between the microscopic world of genes and nerve cells and the experiential and psychological world of symptoms (Braff, Freedman, Schork, & Gottesman, 2007).

Markers and endophenotypes may work in theory, but do they actually exist for schizophrenia? For example, impairment on the Continuous Performance Test (CPT) has been studied as a **cognitive marker** of the disorder.

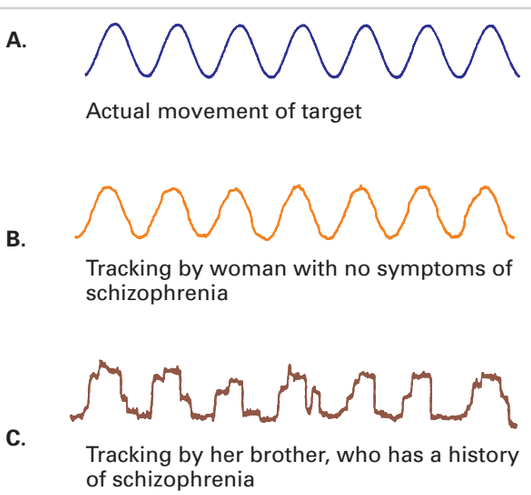


FIGURE 9.1 Samples of Eye-Tracking

Source: Based on Iacono, Bassett, and Jones (1988, p. 1140). Copyright 1988, American Medical Association.

In the CPT, participants observe a string of numbers and are asked to respond (press a button) whenever two identical numbers occur together. On average, patients with schizophrenia consistently score below healthy people on the CPT (Heinrichs & Zakzanis, 1998). This impairment reflects deficits in attention and an inability to keep a rule in mind (working memory). The CPT is also an example of a test that taps an ability that is in part inherited (Hill, Harris, Herbener, Pavuluri, & Sweeney, 2008). However, CPT performance is deficient in only 50 to 60 percent of diagnosed patients. This limits its efficacy as a marker, because it is not sensitive enough to detect the hypothetical disease defect in a large majority of schizophrenia patients.

Another potential marker of schizophrenia involves smooth pursuit eye movements. Due to the controlling influence of attention, our eyes track—or "pursue"—moving stimuli and duplicate the pattern of a continuously moving stimulus in tiny eye movements. Patients with schizophrenia, however, often exhibit irregularities in these eye movements. Their **eye-tracking** records reveal more deviations from the stimulus path, and thus more errors, when compared to a healthy comparison group (Levy, Holzman, Matthyse, & Mendell, 1993); see Figure 9.1. Deficits in eye-tracking may reflect neurological impairments associated with schizophrenia and a predisposition for the disorder. However, once again, even the best eye-tracking indicators are abnormal in only about 50 percent of patients with schizophrenia. Perhaps this task is better suited as a potential marker for a specific variant of schizophrenia or for a broader classification of impairment that includes other psychiatric disorders.

The above examples of potential markers for schizophrenia highlight the difficulty of finding tasks and indicators that are sufficiently sensitive to the disorder. Yet a researcher would not expect 100 percent of the patients in a sample to be abnormal on any given marker task. After all, there may have been errors in diagnosis and some of the patients may not really have schizophrenia. Therefore, some tolerance or allowance for inaccuracy has to be provided. Despite these uncertainties, there is great interest in the discovery of markers and associated endophenotypes that may help to define the disorder more objectively (Oertel-Knöchel, Bittner, Knöchel, Prvulovic, & Hampel, 2011; Schwarz & Bahn, 2008).

COGNITIVE SUBTYPES OF SCHIZOPHRENIA

Cognitive and biological markers are believed to occur in only some patients with schizophrenia because the disorder exists in several variants, forms, or subtypes (Heinrichs, 2004). Instead of defining these subtypes with symptoms, researchers have begun to differentiate them in terms of performance on various neuropsychological tests. For example, subgroups of patients have been identified on the basis of impaired problem solving (Goldstein,

1990; Heinrichs & Awad, 1993) and memory deficits (McDermid Vaz & Heinrichs, 2006; Paulsen et al., 1995; Turetsky, Moberg, & Mozley, 2002). York University researchers showed that patients with schizophrenia could be separated into cognitively impaired, cognitively normal, and verbal memory–impaired subtypes (Ammari, Heinrichs, & Miles, 2010). Patients in the generalized cognitive impairment subgroup experienced the most severe negative symptoms and had the most difficulty adjusting to the demands of everyday life. Hence, cognitive measures may replace symptoms as a tool for the discovery and study of variants and subtypes of schizophrenia.

Etiology

The psychiatric pioneers who described modern schizophrenia at the turn of the twentieth century did not formulate or test hypotheses about the causes of the disorder. Kraepelin (1919) noted the hereditary "taint" of dementia praecox and the fact that it "ran" in families. He also thought that the frontal and temporal lobes of the brain must be involved in the disorder, but never developed these notions into a theory or research program. Bleuler (1911/1950) theorized extensively about the mental life and symptoms of people with schizophrenia without ever grappling in detail with what caused the disorder in the first place. He argued, for example, that disconnected or "dissociated" thinking was a fundamental symptom of the disorder, but offered no suggestions about the causes of the symptom. On the other hand, in the first half of the twentieth century, psychoanalysts (see Chapter 2) made a number of suggestions about the causes of schizophrenia. They argued that experiences during infancy, including emotional traumas and inadequate parenting, could lead to a weak and primitive ego that was unable to distinguish wishes and fears from reality (Fromm-Reichmann, 1959; Reichard & Tillman, 1950; Tausk, 1948). It was believed that a severely rejecting mother could be "**schizophrenogenic**," thereby creating the conditions for a weak and primitive ego—the foundation of schizophrenia—in her children (Diamond, 1997).

The Swiss psychiatrist Carl Jung, working with both Bleuler and Freud, gained considerable experience treating people with schizophrenia. Jung (1956) liked to tell the story of how he "discovered" the connection between psychosis and the **collective unconscious**. One of Jung's patients who had schizophrenia maintained that a swinging penis attached to the sun was the source of the wind. This seemed like just another curious delusion to the psychiatrist until he found a strikingly parallel belief in the ancient Persian religion of Mithraism. The belief held that a swinging tube suspended from the sun caused the wind. Jung became convinced that universal symbols existed in the unconscious mind and erupted into waking life in the course of dreams and mental illnesses like schizophrenia.

In contrast with early views that the disorder primarily reflected internal psychological conflicts and processes, sociological research during the 1930s found connections between schizophrenia and poverty. In particular, first admission rates for the disorder were observed to be four times higher in the slums of central Chicago than in its affluent suburbs (Faris & Dunham, 1939). The relationship between social class and schizophrenia persisted and can be seen in Figure 9.2, which incorporates findings from the 1950s.

One view of the social class–illness link was that the cumulative exposure to poverty, crime, and family disturbances led directly to increased cases of schizophrenia. At the same time, **social drift** explanations held that people from lower socio-economic classes could not rise economically if they had a predisposition for schizophrenia. The predisposition reduced intellectual abilities and motivation even before symptoms occurred, thereby preventing the achievement of educational and occupational goals. While poverty did not turn out to cause the disorder, class-related and other negative social and biological influences may be contributing factors in some cases (Gottesman, 1991). For example, research has revealed that negative immigration experiences in people of colour may contribute to increased development of schizophrenia (Cantor-Graae, 2007). In

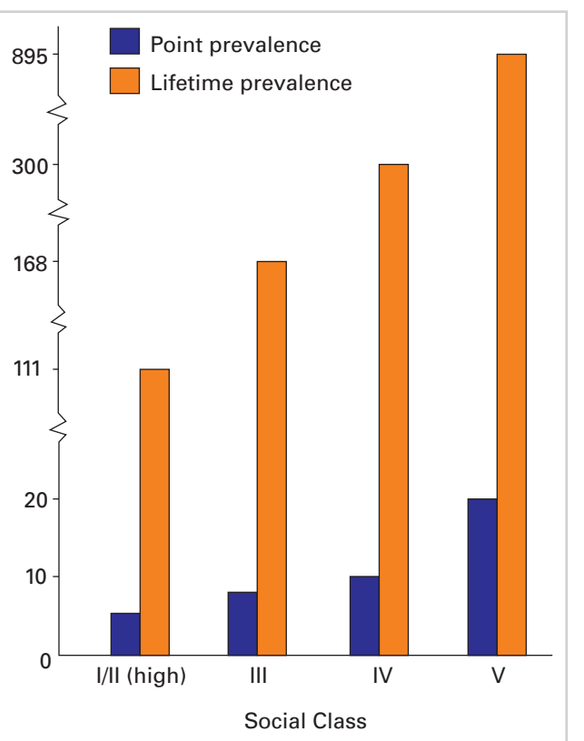


FIGURE 9.2 Prevalence of Schizophrenia by Social Class (rates per 100 000 in New Haven, Connecticut)

Source: Data from Hollingshead & Redlich (1958).

addition, there is evidence that living in a city increases the likelihood that a person already vulnerable to mental health problems will go on to experience psychosis (Dragt et al., 2011). Accordingly, social influences remain an important ingredient in the disorder.

THEORIES OF SCHIZOPHRENIA

In contemporary research, almost no one believes that a mother can cause schizophrenia by rejecting her child or that delusions reflect an eruption of the collective unconscious or that poverty adequately explains the occurrence of severe mental disorders. Instead, complex psychiatric conditions are seen as the outcome of inherited, biologically based vulnerabilities that interact with maturation and development and with life and environmental stresses and influences to push people over a threshold into psychosis. The assumption is that vulnerability, or **diathesis**, and disorder-promoting events, or **stress,** are both required. In addition, the causal pathway from diathesis-stress to clinical disorder is complex and extends over at least the first decade and a half of a person's life. American psychologist Paul Meehl (1962, 1990) built on this assumption and proposed a diathesis-stress theory whereby an inherited gene makes a person vulnerable to schizophrenia. However, whether the disorder actually develops depends on the "good" and "bad" effects of other genes, as well as on the social rewards and punishments experienced by vulnerable people as they grow and change from childhood through adolescence to young adulthood.

MEEHL'S THEORY OF SCHIZOTAXIA, SCHIZOTYPY, AND SCHIZOPHRENIA

The theory proposes a biological diathesis, termed "**hypokrisia**," that occurs throughout the brain, making nerve cells abnormally reactive to incoming stimulation. A single gene inherited from either parent causes this diathesis. However, the "schizogene" is often expressed weakly in a person and its effects may be compensated by other genes, as well as by experience and environmental influences. Hence, not everyone with the schizogene develops schizophrenia. Moreover, even when the gene is expressed in hypokrisia the defect does not interfere with basic, elementary activities of the nervous system. The brain is still able to regulate bodily processes and register, store, and retrieve information. Hence, hypokrisia does not cause mental retardation or other gross disorders of brain function. What it does produce is a subtler disturbance that Meehl called "**cognitive slippage**." Information is disorganized, incoherent, and "scrambled." In Meehl's theory, high intellectual ability can coexist with hypokrisia and cognitive slippage. Yet these defects do distort thinking by causing an exaggerated and persisting tendency to form haphazard connections between ideas, emotions, and events. This "associative loosening" resembles the thought and language disorder described in the section on symptoms. However, in addition, the unselective neuronal firing that causes cognitive slippage gives rise to a gradual increase in punitive, unpleasant social experiences. The brain amplifies feelings of pain and weakens pleasure, making interpersonal relations difficult. This **"aversive drift"** is related to negative symptoms like social withdrawal and disinterest. As the brain scrambles and distorts rewarding and punitive emotional associations, the vulnerable person begins to find social contact more and more unpleasant. Increasingly, such a person avoids social intercourse and is viewed as strange and subject to disapproval by other people. This negative appraisal in turn accelerates the process of withdrawal and creates a vicious circle.

A person experiencing cognitive slippage and aversive drift is termed a "**schizotype**" in Meehl's theory. But such a person may still be spared the full-blown psychotic disorder of schizophrenia. Schizotypal people suffer from "primary" cognitive slippage, difficulty feeling pleasure, social alienation, and other consequences of aversive drift. However, numerous "moderator" genes that influence everything from intelligence to artistic talent to shyness can prevent or accelerate the development of a person's schizotypy into a schizophrenic disorder. In addition, the environment plays a key role in shaping or limiting the expression of schizotypy. For example, schizophrenia becomes more probable when a schizotypal person inherits tendencies toward shyness; anxiety; low energy; weak motivation; and low ability, talent, or physical attractiveness. Even so, these "polygenic" characteristics still have to combine with the influence of a social world that punishes undesirable traits before a person crosses the threshold into a diagnosable schizophrenia spectrum disorder. Conversely, different polygenes may combine in such a way that a person becomes a "compensated schizotype." This is someone who is able to function in everyday life, although usually at a cost to him- or herself or to other people. Meehl mentioned Adolf Hitler as an example of compensated schizotype: an intelligent and talented but socially fearful and inadequate person, prone to incoherent and irrational thoughts and impulses.

According to Meehl, the development of schizophrenia is understandable only as the product of all of these complex influences. Primary hypokrisia, cognitive slippage, and aversive drift are modified or intensified by personality, temperament, and cognitive traits, and this takes place within stressful or supportive social environments.

NEURODEVELOPMENTAL DIATHESIS-STRESS THEORIES

Meehl's formulation has been criticized for its lack of detail on the nature of hypokrisia and cognitive slippage and for not explaining one of the key features of schizophrenia: its occurrence in late adolescence and early adulthood (Heinrichs, 2001). Hence, a number of theorists have accepted the basic diathesis-stress model as a framework and added ideas and detail regarding the nature of what is wrong in the schizophrenic brain, how it got there, and why the disorder occurs primarily in young people.

For example, psychiatrist Daniel Weinberger (1987, 1995) agreed that a person could inherit a genetic defect

APPLIED CLINICAL CASE

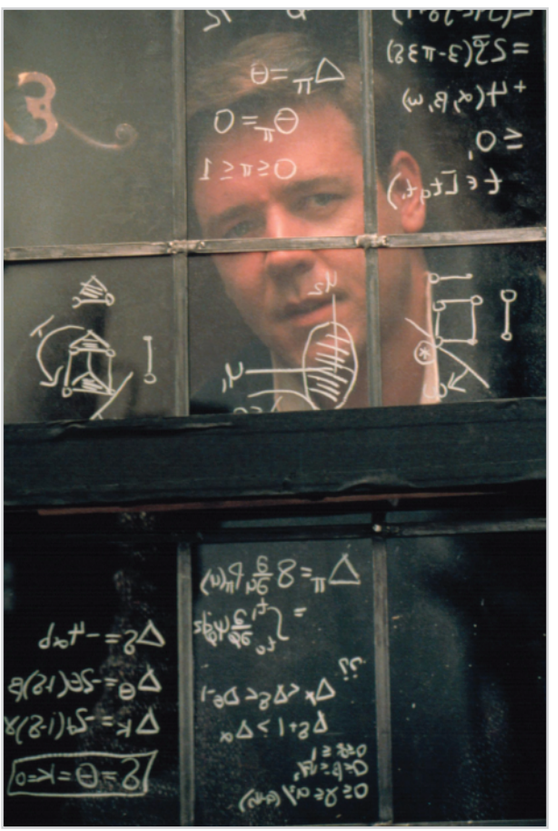
John Nash's Beautiful Mind: When Schizophrenia and Genius Coexist

John Nash was born to well-educated parents in 1928; his father was an electrical engineer and his mother a teacher. Nash showed impressive intellectual potential early in life, carrying out sophisticated chemistry experiments in his room by the age of 10 and proving complex theorems by famous mathematicians at the age of 15. Yet, while intellectually gifted, Nash struggled in social situations. His peers nicknamed him "bug brains" and he came to prefer a solitary lifestyle to the rejection and discomfort often experienced with other people.

Nash's intellectual gifts were expressed in educational and scientific accomplishments. He was offered a full scholarship to complete undergraduate studies at Carnegie Mellon University, where his performance was described as exceptional and extraordinary. He earned a master's degree along with his bachelor of science after only three years of university and was subsequently offered fellowships at both Harvard and Princeton. It was his Ph.D. research at Princeton that eventually won him the Nobel Prize from the Royal Swedish Academy of Sciences.

In his personal life, the odd and peculiar behaviour noticed by many people became even more apparent as Nash completed postgraduate work and pursued further academic interests. Throughout his time at Princeton, he refused to attend classes on principle, instead pacing the halls or riding a bicycle in tight concentric circles. Rather than read in the library, he would lie atop the tables with his hands behind his head. According to Sylvia Nasar, author of *A Beautiful Mind*, a biography of Nash that was the basis for the 2001 movie starring Russell Crowe, these strange character traits marked the path from simple quirkiness to frank psychosis. By the age of 30, after accepting a faculty position at the Massachusetts Institute of Technology (MIT), Nash began hearing voices and developed a delusional way of thinking. He believed that a front-page story in *The New York Times* contained coded messages from inhabitants of another galaxy—messages that only he could unscramble. Later, he offered one of his graduate students an "inter-galactic driver's license" and a seat on his newly organized world government. He wrote thousands of letters to the government, newspapers, and colleagues. Nash believed that everything had meaning and nothing was random or accidental. He would spend days making odd calculations like converting contemporary politician Nelson Rockefeller's name to a complex numerical representation and then mathematically factoring the resulting number.

Perhaps surprisingly, this brilliant and severely troubled man was married, although the couple later divorced. His wife initially attempted to hide Nash's psychiatric problems, but ultimately brought him to hospital against his will. Like many people suffering from schizophrenia, Nash denied his illness, convinced that he was being persecuted. At the time of his first hospitalization, he was diagnosed with paranoid schizophrenia. During this time, treatments for psychotic illness were primitive and usually ineffective (see the section "Treatment" later in this chapter). They included psychodynamic psychotherapy, which has since lost favour as a therapy for psychosis, and insulin shock therapy, long abandoned in favour of medication.



Although his groundbreaking research was probably done before his illness, Nash's case illustrates the possibility that exceptional intellectual ability and achievement can exist in people with schizophrenia. The vast majority of patients with the diagnosis are cognitively impaired, but recent studies reveal that a small number have above-average abilities, especially in verbal skills like vocabulary (Heinrichs et al., 2008). Yet, like Nash, these exceptional patients have difficulty functioning normally in the community. It seems that intellectual ability cannot compensate completely for the devastating experience of severe mental illness. Moreover, even the most gifted patients often face social obstacles like stigma. Indeed, the stigma and negative image of schizophrenia almost prevented Nash from being awarded the Nobel Prize. Many involved with the prize were concerned that giving a prestigious award to a "madman" would embarrass and discredit the Academy of Sciences.

John Nash's experience is unique and atypical compared to most people suffering from schizophrenia, but his amazing story is a testimony to hope, courage, and perseverance in the face of both mental illness and social disapproval.

that creates vulnerability for the disorder. But he believed it was also possible that subtle brain injuries during fetal development or birth could become a diathesis. In theory, this early damage or lesion may occur in brain regions that normally mature in adolescence, when they are required by the emerging demands of social life and sexuality. It is the stress of maturational demands on the weakened brain that precipitates a psychotic crisis and initial hospitalization. Psychologist Elaine Walker (Walker & Diforio, 1997; Walker, Mittal, & Tessner, 2008) has gone further and specified hormone producing and regulating mechanisms in the brain that are normally "switched" on by stress experiences in late adolescence. However, people with the biological vulnerability for schizophrenia cannot cope with the effects of surging stress hormones on brain chemistry and begin to develop symptoms and clinical illness.

All of the diathesis-stress theories of schizophrenia hypothesize a biological vulnerability that is either inherited or acquired very early in life. The vulnerability may take the form of neuroanatomical or neurochemical abnormalities, or both. It is the interaction of these abnormalities with maturation, stress, and life events that eventually causes schizophrenia. Yet although the theories explain why the disorder occurs, to what extent are these explanations supported by the facts? We begin with a consideration of genetics and the role of inheritance in the etiology of schizophrenia.

3 BEFORE MOVING ON

How does the concept of diathesis, or vulnerability, differ from the concept of cause?

BIOLOGICAL FACTORS

IS SCHIZOPHRENIA INHERITED? On the basis of shared genes, human characteristics from eye colour and height to illnesses like diabetes and heart disease "run" in families. Indeed, most psychiatric, behavioural, and medical disorders are under at least some genetic influence. This applies to Alzheimer's disease, autism, major mood disorders, and reading disability, as well as to epilepsy, peptic ulcer, and rheumatoid arthritis. In addition, within the spectrum of normal behaviour, genes play a role in cognitive abilities like memory and intelligence and in personality traits like neuroticism. Genes even play a role in vocational interests and scholastic achievement (McGuffin, Owen, O'Donovan, Thapar, & Gottesman, 1994; Whitman, 2008). Nonetheless, the degree to which these complex illnesses and traits are actually controlled by genes seldom exceeds 50 percent. In many cases, heritability is much lower. Accordingly, non-genetic factors must be of roughly equal importance in determining the emergence of many psychiatric disorders and complex behavioural traits.

A familial **genetic contribution** to the development of schizophrenia has been assumed since the time of Kraepelin (1913, 1919) and Bleuler (1911/1950). Schizophrenia is observed to recur in some families, with a risk of about 13 percent to the children of a parent with schizophrenia. This compares with a general population risk for the disorder of only about 1 percent (Gottesman, 1991). Hence, having one parent with schizophrenia increases the risk of developing the disorder 13 times. However, even in this relatively "high-risk" situation, about 87 percent of people with a parent who has schizophrenia will remain free of the disorder. This "**familiality**" effect, summarized in Figure 9.3, shows that the likelihood of a person developing schizophrenia is much higher if a biological relative also has the disorder. The risk is highest for someone with an identical, or monozygotic, twin and then falls off stepwise as the degree of genetic relatedness diminishes.

Yet the genetics of schizophrenia contrast with disorders like Huntington's disease, which has a more straightforward pattern of inheritance. Defects in a single gene cause Huntington's disease, giving rise to a predictable risk: a 50 percent chance of developing the disease if a person has one parent with the disorder, and a 100 percent chance in the unlikely event that both parents are ill. Complex behavioural syndromes, including psychiatric disorders like schizophrenia, do not follow such patterns of inheritance. For example, if a single gene caused schizophrenia, the risk for illness should decrease by a constant factor of 50 percent between different relative classes. This prediction is based on the degree of shared genetic material in relatives, which ranges from 100 percent in the case of identical twins, to 50 percent for parents, to 25 percent for second-degree relatives like aunts and uncles. However, the risk of schizophrenia for someone who has an identical twin with the disorder is only about 48 percent instead of 100 percent. If all genes are in common, including the one that causes schizophrenia, both identical twins should become ill.

Discrepancies between predicted and observed cases of genetic illness can be dealt with through the principle of incomplete "**penetrance**." In other words, it is known that a proportion of people with a dominant gene will fail to show the effect of that gene. As suggested by Meehl's theory, the lack of expression may be due to the environment or to other factors in the person's genetic constitution. Hence, the penetrance of the schizophrenia gene may be much less than 100 percent and closer to about 50 percent. This roughly fits the risk of the disorder in identical twins. However, the single gene model still does not work for the other relative classes. First-degree relatives should have a risk for schizophrenia of about 25 percent, but Figure 9.3 shows that the observed risks are much lower. Similarly, second-degree relatives should have a risk of 12.5 percent and not the 3 to 4 percent actually observed.

SEARCH FOR "SCHIZOGENES" Evidence against simple gene models also comes from attempts by molecular biologists to link schizophrenia with single genes and specific chromosomes. These attempts have been consistently unsuccessful (O'Donovan & Owen, 1992, 1996). All in all, the idea that one major gene causes schizophrenia is both contradicted by the facts and rejected by most researchers.

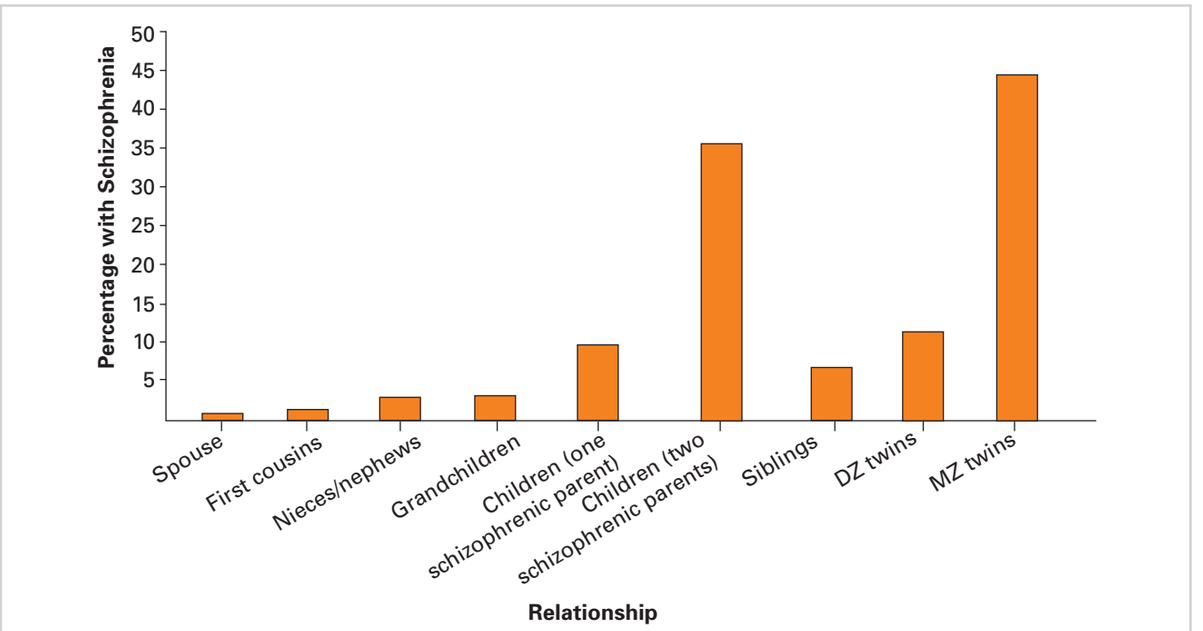


FIGURE 9.3 Prevalence of Schizophrenia Among Relatives of People with Schizophrenia

Source: McGue, M., & Gottesman, I. I. (1989). A single dominant gene still cannot account for the transmission of schizophrenia. *Archives of General Psychiatry*, 46, 478-479; Gottesman, I. I., McGuffin, P., & Farmer, A. E. (1987). Clinical genetics as clues to the "real" genetics of schizophrenia: A decade of modest gains while playing for time. *Schizophrenia Bulletin,* 13, 23-47.

Over the last decade, research has moved increasingly to complex multiple gene models in accounting for the inheritance of schizophrenia (see Gottesman, 1991; Pogue-Geile & Gottesman, 1999; Tiwari, Zai, Müller, & Kennedy, 2010). The field of molecular genetics is considering the possibility that several genes influence the development of schizophrenia. There is evidence for "risk" genes located on chromosomes 1, 2, 3, 4, 5, 6, 8, 9, 11, 13, 15, 16, 17, 18, and 22! Unfortunately, the evidence has sometimes been difficult to reproduce (Kendler, 2000). In addition, individual risk genes have extremely small effects, which means that finding them requires the study of very large numbers of patients (Tandon, Keshavan, & Nasrallah, 2008). For example, any specific gene variant increases the lifetime risk of developing schizophrenia from the general population rate by only about 1 to 1.5 percent. Current approaches compile results from thousands of cases and include the role of environmental influences, while also pursuing new leads like the concept of endophenotypes discussed earlier (Burmeister, McInnis, & Zöllner, 2008). Recent work is considering the possibility that the mechanisms that control or influence genes and their effects may be as important for the etiology of schizophrenia as the genes themselves. These "**epigenetic**" mechanisms may be helpful in explaining why identical twins with the same genes seem to differ in their vulnerability to schizophrenia. For example, Toronto-based researcher Arturas Petronis (2004, 2010) at the Centre for Addiction and Mental Health has identified processes that "turn" genes "on" or "off," and this regulation may be crucial in determining whether a twin actually develops schizophrenia. Accordingly, although schizophrenia is regarded as a highly heritable disorder, unravelling the biological details of the complex genetics involved will challenge researchers for many years to come.

DO PREGNANCY AND BIRTH COMPLICATIONS PLAY A ROLE IN SCHIZOPHRENIA? The diathesis-stress approach to understanding etiology assumes that a genetic predisposition is only part of the pathway that eventually causes an illness. There must be "stressors" as well, including other biological or environmental and social events that accumulate and propel the vulnerable person toward schizophrenia. One possible stressor is a mother's exposure to common viruses like influenza, or "the flu," during pregnancy. Such exposures are linked with increased risk of schizophrenia in the offspring. For example, there is evidence that exposure to the flu virus during the fifth month of pregnancy is associated with an increased risk of schizophrenia in the mother's children later in life (Limosin, Rouillon, Payan, Cohen, & Strub, 2003). However, the incidence of the disorder in people exposed to the virus is still extremely low and some studies have failed to support the relationship (Sacker, Done, Crow, & Goldberg, 1995). Perhaps viral exposure is one of many potential stressors that interact with genetic predisposition and other factors to influence etiology.

Birth-related complications have been proposed as one of these "other" factors. Medical and delivery-related problems at birth may be key environmental and biological events that interact with a genetic diathesis and further predispose a person to schizophrenia. If this idea is true, then

high rates of birth complications should occur in children who go on to develop the illness. Birth complications can be studied by interviewing adult patients and their relatives with respect to obstetrical events and by examining birth and health records if these are available. Complications include prolonged labour, preterm delivery, low birth weight, fetal distress, and breathing difficulties. Indeed, it turns out that such complications are more common in the birth records of people with schizophrenia (Cannon, Jones, & Murray, 2002). However, once again, most people with the illness do not have these abnormalities, even though they occur more often than expected by chance or in comparison to healthy people (Heinrichs, 2001; Tandon et al., 2008).

CAN VULNERABILITY TO SCHIZOPHRENIA BE OBSERVED IN CHILDREN? Viral exposure during pregnancy and complications during birth are two possible events that may combine with genetic predisposition to increase the risk for schizophrenia. If genes and physical events in the environment combine to cause a vulnerability to the disorder, perhaps this vulnerability can be seen in children and adolescents before they experience symptoms. The question of whether early signs of eventual schizophrenia exist seems a simple one, but there are many difficulties involved in answering it. The most serious difficulty is the absence of a dependable, accurate way of identifying in advance who will go on to have the clinical disorder. Nevertheless, researchers have useful, if imperfect, ways of identifying children who have a greater-than-average likelihood of developing the disorder.

One strategy makes use of the fact that the child of a parent with schizophrenia has at least 10 times the normal risk of developing the disorder. Yet even with a large number of **"high-risk" children** to maximize the number of eventual patients, a researcher may have to wait for 20 years to discover which children actually develop the disorder. To counter this problem, some researchers use the "follow-back" approach, which begins with patients known to have schizophrenia in adulthood. Developmental histories, archival documents like hospital records, interviews with living relatives, and even early home movies are then employed to look back in time and find evidence of disturbed mental life and behaviour during infancy and childhood. The main disadvantage of the follow-back method is the limited availability and variable accuracy of old records (and old memories).

Nonetheless, despite the procedural challenge, evidence has accumulated that the liability for schizophrenia does manifest itself, albeit weakly and variably, in a variety of early behavioural abnormalities. A few studies suggest that a proportion of children at risk for schizophrenia show early signs of impaired movement and fine motor skills (Walker, Savoie, & Davis, 1994) and have cognitive limitations not shared by children without this risk (Erlenmeyer-Kimling et al., 2000; Steffy, Asarnow, Asarnow, MacCrimmon, & Cleghorn, 1984). Moreover, some children who are vulnerable to schizophrenia are withdrawn and socially reclusive, or more antisocial and aggressive than non-vulnerable children (Davidson et al., 1999). Overall, by the age of 16, nearly a third of individuals who go on to develop psychotic disorder have motor difficulties and deficient IQs (Dickson, Laurens, Cullen, & Hodgins, 2011).

It must also be that experience in some way shapes the mind and behaviour of those children who later become ill and, as Meehl (1990) acknowledged, this experience is partly psychological and social in nature. There is recent evidence that traumatic experiences in childhood are associated with psychotic experiences later in life, especially in adolescents who also use marijuana (Harley et al., 2010). Furthermore, although parenting and family experiences do not *cause* the disorder, there is evidence that family hostility, lack of support, critical attitudes, and over-involvement may make schizophrenia worse, or at least promote relapses and adjustment difficulties (Hooley, 2007). These negative interpersonal communications directed at the family member with the disorder are referred to as **expressed emotion.** However, expressed emotion also occurs in the families of people with mood (Chapter 8) and eating disorders (Chapter 10). This implies that negative family attitudes may make adjusting to psychological problems difficult in general rather than only in relation to schizophrenia.

Overall, the idea of a **cumulative liability** for schizophrenia that shows itself early in behaviour and increases with adverse environmental events and stresses over the course of childhood and adolescence is very appealing. Such a perspective can make up for the apparent weakness of individual stresses and vulnerabilities because it is the accumulation of liability, and not single events, that is causal. However, the research findings do not amount to a very powerful collection of disorder-promoting diatheses and stresses at the present time. Therefore, researchers have looked into the brain to find abnormalities that may contribute to the cause of schizophrenia.

4 BEFORE MOVING ON

If genes have a major influence on who develops the disorder, why do most children of a mother or father with the disorder never develop schizophrenia?

IS SCHIZOPHRENIA A BRAIN DISEASE?

Neuropsychological Tests. If schizophrenia is a brain disorder, then part or all of the brain must be abnormal in some way, giving rise to the typical symptoms of the disorder. One of the first regions that interested researchers was the **frontal**, or prefrontal, **lobe** of the brain. This large region includes about a third of the brain and has extensive connections with other structures and regions. The psychiatric pioneers believed that psychological capacities ascribed to the frontal brain were impaired in schizophrenia (e.g., Kraepelin, 1913, 1919). A series of case studies of neurological patients with frontal brain damage showed that personality change, impaired self-awareness, loss of initiative, disorganized thinking, impulsivity, and inappropriate

FOCUS 9.3

How Different Are Patients with Schizophrenia from Healthy People?

The explosion of research on schizophrenia across many fields from psychology to neurochemistry means that it is often hard, even for researchers, to arrive at a "big picture" of what is known about the disorder. However, the statistical summarizing technique of **meta-analysis** provides a partial solution to this problem. Meta-analysis, also called quantitative research synthesis, compiles all published articles in a field and transforms the individual results into an overall statistic termed the **effect size**. In the case of schizophrenia research, the effect size reflects the degree of difference between patients and healthy people in terms of any selected psychological or biological comparison. Average effect sizes can in turn be used to estimate the proportion or percentage of patients falling outside the healthy range, which is a statistical way of defining "abnormality" (see Chapter 1). A ranked summary of these "abnormality estimates" is presented in Table 9.3.

TABLE 9.3 ASPECTS OF BRAIN AND BEHAVIOUR MOST FREQUENTLY ABNORMAL IN PATIENTS WITH SCHIZOPHRENIA

Rank	Finding	Frequency (%)
1	slowness writing symbols paired with numbers (processing speed)	71–75
2	poor physical coordination and control (neurological soft signs)	68–78
3	impaired ability to filter out redundant information (sensory gating)	63–80
4	impaired learning and recall of words and stories (verbal memory)	62–75
5	increased neurotransmitter receptors in post-mortem brain tissue (dopamine)	47–81
6	blocking of one sensation by the presence of another (backward masking)	46–76
7	impaired ability to attend to one message and ignore another (dichotic listening)	50–71
8	impaired general intellectual ability (IQ)	50–67
9	reduced ability to generate words rapidly (phonemic word fluency)	53–64
10	slow and inaccurate detection of specified letters (Continuous Performance test)	52–62

Source: Chan, Xu, Heinrichs, Yu, & Wang, 2010; Davidson & Heinrichs, 2003; Dickinson, Ramsey, & Gold, 2007; Heinrichs, 2001, 2005; Heinrichs & Zakzanis, 1998).

Note: The table shows frequency estimates of different research findings based on meta-analytic findings and average effect sizes.

social behaviour were common consequences of damage to this brain area (Ackerly & Benton, 1948; Brickner, 1934, 1936; Harlow, 1848, 1868; Hebb & Penfield, 1940). These features echoed the thought and language disorder, bizarre behaviour, and negative symptoms seen in many patients with schizophrenia. At least on the surface, there were impressive similarities between schizophrenia and frontal brain disease.

Although few researchers believe that schizophrenia can be explained completely as a form of frontal brain disorder, the frontal hypothesis remains one of the earliest and most consistent attempts to relate the disorder to a specific brain system. One research strategy is to give patients with schizophrenia cognitive or **neuropsychological tests** that activate and depend on the frontal region (see Chapter 4). Impairment on such a test supports the hypothesis that the frontal brain is defective in the disorder. Some of these tests are relatively simple and others are more complicated and challenging. For example, one common deficit of frontal brain disease is an inability to generate words rapidly and fluently. According to studies with healthy people, the average person can come up with a total of 30 to 35 words that begin with letters like "F," "A," and "S" in three one-minute trials (see Lezak, 1995). Canadian neuropsychologist Brenda Milner (1964), working at the Montreal Neurological Institute, initiated studies showing that patients with surgical removal of frontal brain tissue generated very few words. The "FAS" technique was subsequently applied to patients with schizophrenia and compared to healthy people in 27 separate studies conducted between 1980 and 1997. There was a consistent deficiency in the patient samples, with results suggesting that a clear majority of patients produced fewer words than healthy people (Heinrichs, 2001).

Another neuropsychological test also applied originally by Milner to patients with frontal damage is the **Wisconsin Card Sorting Test** (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993). Most versions involve presenting four "key" cards that depict different shapes, colours, and quantities. The person taking the test is provided with a succession of cards and asked to match each one to a key card. Cards may match on the basis of colour, shape, or number, but only one matching principle is "correct" at a given time. The examiner controls the matching principle

and gives feedback about the correctness of each attempted match without ever disclosing the actual principle. Then, after a succession of correct matches, the examiner changes to a new principle (e.g., shape instead of colour) without telling the test-taker. The object of the test is to discover the new principle each time it changes and to respond with correct matches. The WCST is easy for healthy people with average intelligence, but Milner (1963) showed that patients with prefrontal brain damage achieved abnormally few successively correct matches or "categories." They also tended to repeat or **perseverate** erroneous responses.

The WCST has proven to be the most popular neuropsychological measure in schizophrenia research, used in 43 studies published between 1980 and 1997 (Heinrichs & Zakzanis, 1998). Cumulative results from these studies show that at least half of patients with schizophrenia are consistently impaired relative to healthy people. Moreover, this deficiency is similar in severity to the results of studies conducted with neurological patients who had documented damage to their frontal lobes (Heinrichs, 2001).

Despite this impressive evidence, neuropsychological tests do not provide definitive support for the **frontal brain deficiency** hypothesis in schizophrenia. Most tests are sensitive to more than one brain region, so that poor performance does not necessarily mean that the frontal region, or only the frontal region, is defective. Indeed, many neurological patients without frontal damage also find the WCST hard, and some patients with frontal damage manage to obtain surprisingly good scores (Anderson, Damasio, Jones, & Tranel, 1991; Heaton et al., 1993). Another problem is that poor performance on any single test may be a product of a much more general impairment likely to affect most aspects of cognition and performance. As a group, individuals with schizophrenia have lower IQs than the general population, and this broad intellectual disadvantage may also reveal itself in any individual cognitive test result (Heinrichs & Zakzanis, 1998). Thus, at least some of the time, researchers may be measuring a broad ability factor that depends on the whole brain when they think they are measuring only frontal brain abilities. Clearly, the question of whether the frontal brain contributes to schizophrenia cannot be resolved with neuropsychological tests alone. Fortunately, the same question can be addressed with biological methods that offer a much more direct picture of frontal brain structure and physiology.

PICTURES OF THE LIVING BRAIN

Description of Structural Techniques. Developments in brain scanning and imaging over the last three decades provide remarkably accurate ways of studying brain biology (see Chapter 4). First, there are imaging techniques that yield a visual or quantitative display of neuroanatomical structure—a picture of the living brain. These techniques include computerized axial tomography (CT) and **structural magnetic resonance imaging (MRI)**. MRI, in particular, is able to provide clear, detailed images of many brain structures. Since schizophrenia does not involve obvious brain damage like strokes or tumours, most structural brain imaging research compares the volume and shape of different brain regions in patients and healthy people. The assumption is that abnormally small regions must have sustained some kind of damage, including, for example, nerve cell losses. Alternatively, the brain may not have developed normally in the first place, creating vulnerability for schizophrenia later in life.

Findings from CT and MRI Studies. Using these techniques, researchers have found complex patterns of structural abnormalities in patients with schizophrenia, compared with healthy individuals. One of the earliest CT findings suggesting structural alterations in the brains of patients with schizophrenia was that the ventricles are larger than those in non-psychiatric brains (Johnstone, Crow, Frith, Husband, & Kreel, 1976). In particular, the third and lateral ventricles are expanded, which suggests compression or loss of existing nerve tissue. In MRI studies, the most consistent findings include reduced grey matter volumes of the medial temporal, superior temporal, and prefrontal areas (Karlsgodt, Sun, & Cannon, 2010). These are regions on which episodic memory, processing of auditory information, and short-term memory/decision making, respectively, are critically dependent. Other reported structural differences in patients with schizophrenia include parietal lobe, basal ganglia, corpus callosum, thalamus, and cerebellar abnormalities (Kasai et al., 2002; Niznikiewicz, Kubicki, & Shenton, 2003; Shenton, Dickey, Frumin, & McCarley, 2001).

Description of Functional Techniques. More recent advances in imaging technology extend traditional anatomical imaging to include maps of human brain function. These "functional" imaging techniques include **positron emission tomography (PET)** and **functional magnetic resonance imaging (fMRI).** PET scanning involves the introduction of a mildly radioactive tracer into the bloodstream of a person and the use of a sensory apparatus, a kind of camera, to detect the tracer's presence and distribution in the brain. Depending on the type of tracer, this method can furnish a display or readout of changes in blood flow, the metabolism or rate at which energy is used, or the location and density of nerve cells containing specific kinds of chemical receptors. Brain regions with higher activity levels use more blood and will have increased levels of the radioactive tracer that will be detected and imaged by the camera.

On the other hand, fMRI works by detecting the changes in blood oxygenation and flow that occur in response to neural activity. When a brain area is more active, it consumes more oxygen, and to meet this increased demand, blood flow increases to the active area. fMRI techniques allow for the production of activation maps showing which parts of the brain are involved in a particular mental process after controlling for brain activity at rest (see Figure 9.4). These most recent technologies have been applied increasingly to schizophrenia over the last decade (see Huettell, Song, & McCarthy, 2008).

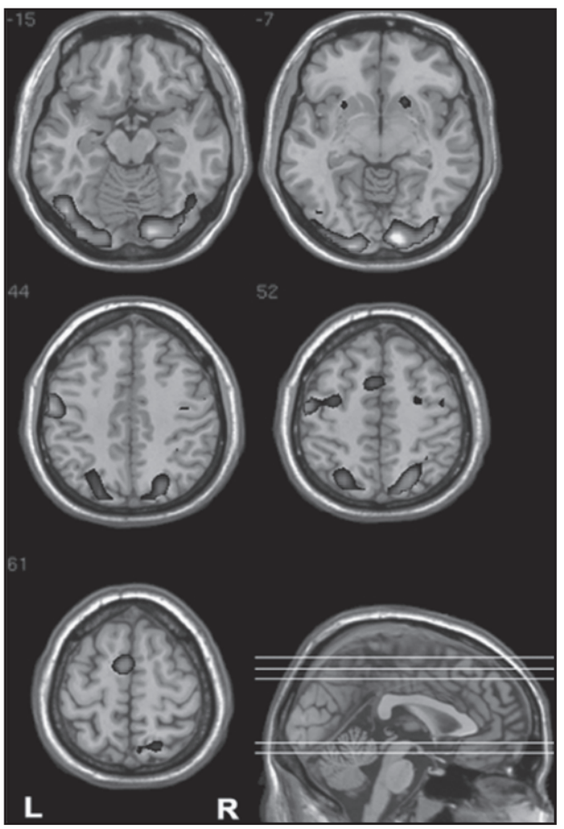


FIGURE 9.4 fMRI Images Showing Regions of Activation During Short-Term Memory Task in Normal Brain

Regions of increased brain activation appear when the person being scanned has to remember small amounts of information over periods of seconds or minutes. Together, these "hot spots" of activity may form a short-term memory network. This network seems to operate less efficiently in people with schizophrenia. The lower-right diagram shows the locations or fMRI "slices" through the brain.

Source: Cairo, Woodward, & Ngan (2006).

Findings from PET and fMRI Studies. In addition to structural changes, functional activation changes, as measured by both fMRI and PET, have been well documented in patients with schizophrenia. To what extent, then, do these brain imaging techniques support the idea that schizophrenia is a disorder of the frontal brain? Lara Davidson, a former graduate student in clinical psychology at York University in Toronto, compiled the findings of all available studies published between 1980 and 2002 (Davidson & Heinrichs, 2003). The results of this meta-analysis showed that only about 25 percent of schizophrenia patients have abnormally reduced frontal brain volumes, and less than 50 percent have reduced blood flow or metabolism in the frontal region when engaged in a mental "activation" task. One way of interpreting this outcome is to say that frontal brain impairment probably affects *some* patients with schizophrenia, but the impairment is not a *necessary* part of the syndrome. It is also possible that only the negative symptoms of the disorder reflect an abnormally working frontal brain. In any case, many patients cannot be distinguished from healthy people with structural MRI or functional PET imaging. Of course, as the use of more accurate and informative techniques like functional MRI increases, the evidence in support of the frontal hypothesis may change. For example, recent findings suggest different patterns of frontal brain activation and deactivation in schizophrenia rather than just an overall reduction (Pomarol-Clotet et al., 2008). Several other brain regions are also of interest in relation to schizophrenia. One of the most researched regions includes the **left temporal lobe** and its many connections with other regions, including the frontal lobes. This is a psychologically vital brain region that controls aspects of attention, the understanding of speech and written language, and interpretation of the visual world. It is in the temporal brain system that sounds are recognized as words, and light patterns as pictures, objects, or human faces. Associated structures like the **amygdala** and **hippocampus** colour these interpretations with emotion and store them in memory. Neurological patients with damage in this region have deficits like receptive aphasia, which means they are unable to understand spoken and written language. Patients with deeper damage affecting the hippocampus are unable to form new memories of events, although memory for the remote past may be relatively intact. Kraepelin (1913, 1919) and other psychiatric pioneers knew the psychological importance of the temporal brain region in broad terms and suggested that, along with the frontal brain, the temporal lobes were the place to look for the causes of schizophrenia.

The evidence compiled and summarized using meta-analysis shows that some psychological abilities associated with the left temporal lobe, especially memory, but also selective attention, are probably deficient in up to 75 percent of individuals with schizophrenia (see Focus box 9.3 and Table 9.3). Conversely, only a small proportion of patients may have normal attention and memory abilities. However, evidence based on brain imaging (MRI, PET) and more direct measurement of the temporal region tells a somewhat different story. None of these comparisons detect abnormalities in a large proportion of patients, and hence they were not included in the summary table. Indeed, meta-analysis shows that the volume of the left temporal lobe is reduced in only about 21 percent of patients, although approximately 38 percent have an abnormally small hippocampus. The results for altered blood flow and metabolism are complex and inconsistent, partly because "resting" and "activation" studies produce different results. Yet here too the evidence in favour of neurobiological abnormalities is not impressive. The average resting activity of the left temporal lobe seems almost the same in patients and healthy people on the basis of PET brain scanning results. Only about 8 percent of patients have truly abnormal blood flow and metabolism. The proportion rises to about 27 percent when temporal lobe activity during a cognitive task is measured. In addition, this proportion of patients seems to have an abnormally

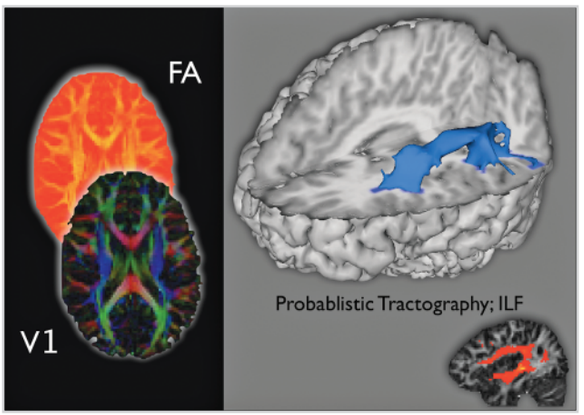


FIGURE 9.5 Diffusion Tensor Imaging (DTI)

DTI allows for the examination of white matter connectivity in the brain. Several techniques are available to analyze the data obtained using DTI. These images include fractional anisotropy (FA) on the left, which indicates the presence and direction of white matter tracts, and a form of brain mapping called tractography on the right, which shows the beginning and end of a predetermined connective tract of interest, in this case the inferior longitudinal fasciculus (ILF).

Source: Images generated using FMRIB Software Library: FSL tools 4.1.9: (FDT & Probabalistic Tractography). Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E.J., Johansen-Berg, H., Bannister, P.R., DeLuca, M., Drobnjak, I., Flitney, D.E., Niazy, R., Saunders, J., Vickers, J., Zhang, Y., De Sefano, N., Brady, J.M., & Matthews, P.M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, 23 (S1), S208-S219.

overactive rather than underactive left temporal lobe. It is noteworthy, however, that many PET findings have poor records in terms of being reproduced by several investigators. In fact, no brain imaging findings make the "top 10" list of findings presented in Table 9.3.

What does this often weak and at times inconsistent evidence indicate about the biology of schizophrenia? It must be that brain regions mediating the perception and storage of meaning and the creation of emotional associations are also the regions involved in schizophrenia. However, research has not demonstrated this involvement in a very convincing way, at least not yet. It is cognitive performance and abilities that appear to be most severely compromised by the disorder, whereas biological findings are often abnormal in only a minority of patients. Is it possible that technical limitations, rather than a faulty hypothesis, underpin the weakness of neurobiological findings on both the frontal and temporal brain hypotheses? Perhaps the brain scanners are at fault. They still lack the degree of accuracy needed to detect the kind of microscopic neural abnormalities that underlie the disorder. However, the near future may hold the answers. For example, recent applications of fMRI indicate that different fronto-temporal brain networks perform abnormally depending on the specific kind of cognitive task presented to patients with schizophrenia (Kuperberg, Lakshmanan, Greve, & West, 2008).

A recent extension of MRI technology, diffusion tensor imaging (DTI), has allowed for the examination of connectivity in the brain (see Figure 9.5). DTI is a critical advancement in neuroimaging, given that brain regions rarely act in isolation. Rather, the brain is a complex organ with component structures that are highly interconnected. The application of DTI to schizophrenia research is fitting because the disorder may involve disturbed communication between and within regions. DTI is based on the idea that water molecules behave differently in connective white matter compared to other brain tissue. Images can be developed using DTI that index white matter fibre tracts that connect brain regions. Recent reviews of DTI studies in schizophrenia have also implicated frontal and temporal regions. Specifically, studies have found that connective tissue or tracts like the corpus callosum, cingulum bundle, and internal capsule are the areas of the brain most affected in schizophrenia (Kyriakopoulos, Bargiotas, Barker, & Frangou, 2008).

The next generation of imaging developments may furnish the powerful evidence of fronto-temporal brain involvement in schizophrenia that is currently lacking. Many brain regions and their connections are under study and the field continues to await a succession of strong findings that converge on the same region (see Harrison, 1999). However, it is also possible that part of the schizophrenia puzzle lies in the brain's chemistry.

IS SCHIZOPHRENIA CAUSED BY A NEUROCHEMICAL IMBALANCE?

The arrival of the first therapeutic drug treatments for psychotic symptoms during the 1950s inspired researchers to study schizophrenia as a biological disease. If a chemical agent like a drug was able to reduce symptoms, it might be because brain chemistry was abnormal in the disorder. Perhaps schizophrenia consisted of an abnormality in neurotransmission—the chemical transactions that compose communication between nerve cells at the molecular level. In addition to smaller or malformed brain regions and altered patterns of blood flow and metabolism, the causes of schizophrenia might involve an abnormality or alteration in neurochemistry.

The Dopamine Hypothesis. Researchers in the early 1960s identified a group of brain chemicals involved in the therapeutic effects of antipsychotic drug action. This research showed that **dopamine**, a member of the catecholamine family of **neurotransmitters**, plays a major role in therapeutic drug effects. More specifically, the clinical efficacy of antipsychotic drugs is correlated with their ability to block the effects of dopamine. The hypothesis that dopamine is central to schizophrenia has been one of the most enduring ideas about the disorder. The strongest support for a connection between abnormal dopamine activity or dysregulation and schizophrenia comes from studies showing that antipsychotic drugs like chlorpromazine reduce symptoms by blocking dopamine **receptors**, especially the dopamine D2 receptor subtype. Canadian researcher Dr. Phillip Seeman at the University of Toronto carried out the first studies demonstrating the link between dopamine blockade and symptom reduction (Seeman & Lee, 1975). Seeman used postmortem brain tissue samples from patients with schizophrenia to show that the most effective antipsychotic drugs were chemicals that occupied and blocked receptors for dopamine.

Also supporting the dopamine hypothesis of schizophrenia was the observation that several drugs, including cocaine and amphetamine, accentuate or boost dopamine activity rather than blocking it. This enhancement can induce psychotic symptoms that resemble acute schizophrenic episodes. For example, high doses of cocaine taken by people who do not have schizophrenia may result in persecutory fears and paranoia and create a severely distorted sense of reality (Julien, 2007). Cocaine appears to produce these effects in part by blocking the dopamine transporter, thereby inhibiting reuptake. Concentrations of dopamine in the synaptic space are probably increased in cocaine users, heightening the impact of the neurotransmitter on the post-synaptic neuron. Clearly, there is a correlation between enhanced dopamine activity and psychosis and between blocked dopamine activity and reduced psychotic symptoms.

The evidence on drug effects and dopamine is suggestive, but it does not prove that something is wrong in the dopamine systems of people with schizophrenia or that abnormalities in the neurotransmitter cause the disorder in the first place. However, it is difficult to measure dopamine levels or activity in the brain directly in living people. Therefore, researchers have taken advantage of the fact that the neurotransmitter's byproducts are present in the cerebrospinal fluid (CSF) that surrounds the brain and circulates into the spine. Samples of this fluid can be drawn from the spinal canals of patients and healthy research participants, providing a kind of index of dopamine activity in the brain. The logic is that patients with schizophrenia should have greatly increased levels of these byproducts, reflecting the presence and use of large quantities of dopamine. However, dopamine metabolites were not universally elevated in the CSF of patients with schizophrenia. Furthermore, virtually no differences between patients and healthy people have emerged (Heinrichs, 2001). Accordingly, interest moved to the dopamine receptors that are blocked by antipsychotic drugs. Perhaps schizophrenia does not involve abnormal amounts of dopamine itself as much as it involves abnormal concentrations of dopamine receptors. But how could these microscopic substances be detected and measured?

By the late 1970s, chemical "labels," or **ligands**, that bind selectively with specific receptor sites became available (Seeman, Chau-Wong, Tedesco, & Wong, 1976). This gave rise to a new kind of study, the radioactive binding assay, wherein the density and distribution of various receptors were determined. First, the ligand was labelled with a radioactive isotope. Next, tissue samples from preserved post-mortem brain tissue obtained from schizophrenia patients, or from healthy people who died of natural causes, were prepared in the form of slices. These slices were then exposed to the ligand, which in turn occupied the receptor sites. The end of several technical steps was a display showing the location and density of receptors in the treated brain section. A magnifying glass had been placed over the microscopic world of the dopamine receptor.

Over a 15-year period, researchers looked for evidence that dopamine receptors were abnormally elevated in the brains of people with schizophrenia. Initial findings like those by Lee and Seeman (1980) were promising, with a majority of patient samples showing increased dopamine receptor densities. However, it was also known that these tissue samples were obtained from patients receiving antipsychotic medication prior to death. There was evidence that dopamine-blocking medication stimulated the brain to make more dopamine receptors. Accordingly, chronic exposure to antipsychotic drugs during life may have caused an artificial increase in receptor numbers and distorted the results of receptor assays of schizophrenic brain tissue samples. Although efforts were made to obtain tissue samples from patients who were drug free for weeks or months prior to death, it was hard to completely rule out lifetime drug exposure as an artificial influence on receptor-binding studies. What researchers needed was a way of measuring the density of dopamine receptors in the brains of living patients with schizophrenia.

This possibility was realized with the application of receptor-binding ligands to the field of PET scanning. Instead of injecting tracers that bound to blood cells or glucose, researchers introduced the ligands that bound to dopamine receptors. The innovation not only meant that living people could be studied, but also that individuals who had never been treated with antipsychotic medication could be examined. The PET receptor-binding methods provided the opportunity to determine if schizophrenia involved elevated dopamine receptors without the distorting influence of **dopamine-blocking drugs**. Initial results (Gjedde & Wong, 1987; Wong et al., 1986) confirmed that a large majority of patients with schizophrenia had dopamine receptor densities exceeding the normal range. However, independent researchers failed to support these findings (Martinot et al., 1990) and the field became mired in controversy. It was unclear whether technical properties of different ligands, the imperfect accuracy of PET scanning equipment, or different samples of patients were responsible for the inconsistent results (Sedvall, 1992).

Since the early 1990s, the original form of the dopamine hypothesis has been modified in light of the available evidence and advances in neurobiology and brain imaging technology. Davis, Khan, Ko, and Davidson (1991) reconceptualized the hypothesis to specify excess dopamine neurotransmission in the striatum and reduced dopamine neurotransmission in the frontal lobes of the brain. In the most recent revision of the dopamine hypothesis, Howes and Kapur (2009) hypothesize that multiple "hits" (e.g., pregnancy and obstetric complications, stress and trauma, drug use, and genes) interact to result in dopamine dysregulation. The authors claim that this dysregulation is the "final common pathway" to psychosis in schizophrenia. In sum, what was once a simplistic theory about the role of dopamine in schizophrenia is increasingly complex. It has become progressively more apparent over the past several decades that several neurotransmitter systems are likely involved in schizophrenia. For example, another neurotransmitter, serotonin, has been implicated in some of the therapeutic effects

of more recent antipsychotic drugs. Moreover, dopamine interacts with other important neurotransmitters, including glutamate and gamma-aminobutyric acid (GABA), and some researchers suspect that these substances are the true culprits in the story of neurochemistry and schizophrenia (González-Maeso et al., 2008).

5 BEFORE MOVING ON

Is a single biological abnormality found in all patients with the diagnosis of schizophrenia?

Treatment

For many decades following Kraepelin's (1896, 1913, 1919) pioneering descriptions of schizophrenia, there was no effective medical or psychological treatment for the disorder. In fact, use of the term *treatment* to describe what patients endured is highly questionable. Patients with schizophrenia might be subjected to "great and desperate" methods like prolonged barbiturate-induced sleep therapy, **insulin coma,** or **psychosurgery** (Valenstein, 1986). These were "treatments" to be feared and avoided, but patients' rights were seldom at the forefront during the first half of the twentieth century. There were no therapies with proven effectiveness, and experimental procedures were attempted that lacked scientific or medical justification. For example, insulin coma therapy involved creating a hypoglycemic state (low blood sugar) through administration of high doses of insulin. This resulted in loss of consciousness and frequent convulsions. A few reports suggested that a series of such insulin shocks might reduce a patient's psychotic episodes. However, the technique was never carefully evaluated and brought risks to the patient in terms of heart attacks and strokes. Some patients with schizophrenia underwent brain surgery—"psychosurgery"—in the form of **frontal lobotomies** or leukotomies, wherein nerve tracts in the frontal brain were cut. As a hospital psychologist, one of the authors (W. H.) once carried out a neuropsychological assessment with a survivor of this sinister era, an elderly woman who had undergone psychosurgery decades before, in a dim past that she could barely remember. This unfortunate woman was left with brain damage and cognitive deficits due to the surgery—and she retained her schizophrenia. Many thousands of patients were operated on with little demonstrable benefit and little concern for ethical requirements like informed consent to treatment.

By the early 1950s, Canada and the United States had hospitalized on an indefinite basis well over half a million patients with schizophrenia and other severe mental illnesses. Although the psychiatric pioneers had hoped to bring medical science to bear on the problem of schizophrenia, a patient in 1850 may have been better off in terms of quality of life, if not the disease process itself, than a patient in 1950. Fortunately, within a few years this depressing assessment changed as the first genuine treatments for schizophrenia were discovered and developed.

ANTIPSYCHOTIC MEDICATION

The discovery of drugs to treat the symptoms of schizophrenia is a story of accident, dedication, and insight. A young French naval surgeon named Henri Laborit (see Swazey, 1974) was interested in the syndrome of circulatory shock that occurred during and after surgery. The syndrome included depression and apathy, along with marked physical features like shallow breathing and a bloodless, pale appearance. Shock could sometimes progress to death within hours. Laborit and his colleagues began experimenting with a variety of drugs in an attempt to find a compound that might alleviate the shock syndrome in surgical patients. One relatively new agent called promethazine proved to have a number of intriguing and unexpected properties. The drug made patients drowsy, reduced pain, and created a feeling of "euphoric quietude." Hence, promethazine had psychological effects. It was observed that surgical patients receiving the drug remained conscious without signs of pain or anxiety. Laborit realized that if the drug had psychological effects it must be acting on the brain and not just on the circulatory system.

Laborit's (1950) published observations encouraged researchers to modify the formula of promethazine and enhance its curious, brain-related effects. The upshot of these efforts was **chlorpromazine**, the first genuine antipsychotic medication. It was another 10 years before the new drug's specific value in treating schizophrenia was fully recognized and documented. The initial observations of promethazine and chlorpromazine in psychiatric patients reflected the mood-influencing effects that developed over days and initial weeks. Hence, it was thought that the drugs might be most helpful in patients with mood disorders, mania, and agitation. However, it turned out that antipsychotic effects took several weeks to develop fully. A series of drug effectiveness studies or clinical trials was required to demonstrate the full range of clinical applications for the new medication. Canada played an important part in these drug evaluations through studies by Lehmann and Hanrahan (1954) at McGill University in Montreal. Following the large collaborative National Institute of Mental Health study (1964) in the United States, the evidence was finally conclusive. Chlorpromazine reduced more than agitation, mania, and mood disturbances. It also reduced the symptoms associated with schizophrenia.

A large volume of studies now documents the value of chlorpromazine and its chemical relatives, as well as a "new generation" of medications developed in the 1990s, in alleviating the frequency and severity of hallucinations and delusions, thought disorder, and, to a lesser degree, the negative symptoms of the illness. Patients who receive these medications require less time in hospital, have fewer relapses, and enjoy better life functioning when compared to untreated patients (Julien, 2007; Kane, 1989; Meltzer, 1993). However, these drugs are a way of controlling and managing symptoms and not a cure for schizophrenia. Moreover, a minority of patients does not benefit from antipsychotic drugs, and even responsive patients may have

to deal with unpleasant and occasionally disabling side effects. This situation has stimulated the development of improved medications, including **risperidone** and **olanzapine**, that provide symptom control with fewer side effects than the older chlorpromazine family of drugs. Still, many patients experience a return of their symptoms if medication is discontinued or they find prolonged medication use unpleasant. Moreover, drugs may control symptoms, but they cannot provide the occupational and daily living skills or social supports needed to ensure successful adjustment outside of hospital. In fact, the most disabling aspect of schizophrenia may be the cognitive impairment associated with the disorder rather than the positive and negative symptoms. Cognitive impairment plays a major role in limiting skill learning and everyday life functioning. Perhaps not surprisingly, there is intense interest in the development of "cognitively enhancing" medications that can address these impairments (Harvey & Keefe, 2001). The benefit that current antipsychotics have for cognition is very small, especially in individuals with chronic schizophrenia (Keefe et al., 2007). Additionally, both older and more recent antipsychotic medications produce only extremely small improvements in cognition (Heinrichs, 2007).

Discharging patients from hospital may leave them adrift on city streets with nowhere to go, nothing to do, and no means of support. Too often, ex-patients must struggle with poverty, unemployment, and the negative attitudes of other people, or **social stigma.** These challenges have replaced the confinement and dependency of the pre-medication era, and they are poor alternatives to hospitalization for the person with schizophrenia (see Torrey, 1995).

PSYCHOTHERAPY AND SKILLS TRAINING

The use of psychotherapy in the treatment of schizophrenia has been the subject of considerable controversy. Many pioneers in clinical psychology and psychiatry, including Sigmund Freud, argued that psychoanalysis is ineffective for the treatment of schizophrenia. Several research findings pointing to the poor outcomes of psychotherapy for patients with schizophrenia supported this claim. Further, the established effectiveness of medication as a treatment for schizophrenia in the 1960s contributed to the reluctance to employ psychotherapeutic treatment approaches. At the same time, some researchers and therapists have always insisted on the value and effectiveness of psychoanalytically oriented therapies, leading to lively but inconclusive controversies (Karon & VandenBos, 1981). Adding fuel to the fire, several older literature reviews have noted methodological limitations in previous research, thereby calling into question the value of the studies that rejected psychoanalysis for patients with schizophrenia (Beck, 1978; Mosher & Keith, 1980).

COGNITIVE-BEHAVIOURAL THERAPY

More recently, studies of **cognitive-behavioural therapy (CBT)** for patients with schizophrenia have revealed that at least one form of psychotherapy may indeed be helpful in treating this population (Beck, Rector, Stolar, & Grant, 2009; Turkington, Dudley, Warman, & Beck, 2004). Indeed, CBT is now recommended as a standard of care by the National Institute for Clinical Excellence, with a particular focus on four principal problems experienced by psychotic patients: (1) emotional disturbance, (2) psychotic symptoms like delusions and hallucinations, (3) social disabilities, and (4) risk of relapse (Fowler, Garety, & Kuipers, 1995). CBT theory maintains that emotional and behavioural disturbances are influenced by subjective interpretation of life and illness experiences. CBT for schizophrenia integrates analysis and understanding of the patient's symptoms and delusional beliefs through techniques like psychoeducation, belief modification, and coping strategy enhancement (Kingdon & Turkington, 2005). Normalization is one form of psychoeducation, which helps patients understand symptoms by comparing their experiences to those of mentally healthy adults. For example, therapists explain that anomalous experiences can occur in healthy adults who are suffering from sleep or sensory deprivation, or from unusually high levels of stress. Moreover, patients are taught how to interpret correctly relevant environmental events and how to respond appropriately to social cues while interacting and communicating with other people. These techniques are thought to help reduce patients' catastrophic interpretations of symptoms and aid in preventing relapse. Often, therapy develops over a sequence of stages. For example, Canadian psychologist Neil Rector (Beck et al., 2009; Beck & Rector, 2000; Rector, Seeman, & Segal, 2003) focuses initially on engaging the patient with schizophrenia, as a trusting and collaborative therapeutic alliance is critical for success. Establishing this relationship may involve listening, empathic understanding, and gradual exploration of the patient's experiences, combined with gentle questions, which lead to the formulation of a problem list. Next, patients are taught to record and monitor their thoughts and to carry out "homework" assignments. Similar to CBT for depression or anxiety, a thought record or voice diary is often incorporated into treatment to help the patient rationally appraise related symptoms as they occur. For example, recording the intensity and number of voices, affective responses, and self-initiated coping attempts at the time of symptom onset allows the therapist to select novel strategies or improve on existing strategies (i.e., coping strategy enhancement) that will help to reduce symptom severity. Consequently, therapy becomes increasingly focused on the individual's unique clinical presentation, and through careful questioning the patient is encouraged to test the validity of his or her symptoms and to consider their influence on daily life. Alternative explanations are developed for delusions and hallucinations, with belief modification as the final goal of treatment. However, therapists must be careful to maintain a nonconfrontational stance, which often results in therapy progressing at a slow pace. In fact, pushing patients too quickly can result in increases in belief conviction and likelihood of relapse (Nelson, 1997). With respect to negative symptoms, patients are challenged

and assisted in identifying the sources of their inactivity or withdrawal, and they participate in "experiments" to create alternative and more rewarding experiences and new interests. The last phase in a CBT program may involve patients learning to direct their own cognitive skill development and progress with an eye toward preventing symptom relapses and severe illness episodes. In fact, because relapse is common among patients with schizophrenia, therapists often create reminder coping cards for common delusions or hallucinations that can be referred to when symptom reoccurrence is imminent or occurring (Chadwick, Birchwood, & Trower, 1996).

A recent review of the evolution of CBT in schizophrenia (Tai & Turkington, 2009) summarized findings from a body of evidence that highlighted the efficacy of this intervention. The authors reported that moderate benefits are shown for both positive and negative symptoms and that these benefits are sustained over time (Malik, Kingdon, Pelton, Mehta, & Turkington, 2009). Most recently, clinicians and researchers have used CBT to target low-functioning, chronically disordered patients with schizophrenia. Results from an 18-month clinical trial by Grant and colleagues (2011) found that patients receiving CBT showed gains in their psychosocial functioning and motivation and experienced reduced positive symptoms (e.g., hallucinations, delusions, disorganization). Taken together, the findings from these and other studies are promising. However, research on the predictors of response to treatment (e.g., gender, neurocognitive deficit, insight) is still relatively new and inconclusive (e.g., Brabban, Tai, & Turkington, 2009).

SOCIAL SKILLS TRAINING AND COGNITIVE REMEDIATION **Social skills training** is a learning-based intervention model for the treatment of functional disabilities associated with schizophrenia (Chien et al., 2003). Unlike the symptom-focused CBT approaches, social skills training provides rehabilitation for patients with schizophrenia, fostering the development of practical social and living skills. Patients typically receive training in a variety of functional skills, including carrying out appropriate social interaction, coping with common stressors, dealing with household and residential tasks, and developing employment-related abilities. The social skills training approach thus promotes independence and simultaneously reduces stressors.

A recent meta-analysis of 22 randomized controlled trials, a strict method for evaluating treatments, found that social skills training had moderate effects on social and independent living skills (based on role-play measures), psychosocial functioning, and negative symptoms. Small beneficial effects were observed for relapse rates (Kurtz & Mueser, 2008). These interventions were most effective with younger patients. Continued efforts are needed in developing similarly helpful social skills training for older, more chronic patients who make up a significant proportion of the population with schizophrenia.

Cognitive remediation programs have been used with schizophrenia for the past four decades. Interest in this therapeutic approach followed from emerging research on the relationship between cognitive performance and community outcome. These interventions target specific thinking skills like memory and attention by teaching compensatory strategies, providing practice exercises, and holding group discussions, each with the goal of enhancing cognitive ability. Reviews of this growing body of literature indicate that remediation training has significant benefits for improving cognition in schizophrenia, with medium-range effect sizes that are maintained over an eight-month period (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007). Cognitive remediation also demonstrated a significant effect on reducing psychiatric symptoms and improving psychosocial outcomes (e.g., obtaining competitive work or more satisfaction with interpersonal relationships). These effects appear to be even stronger when cognitive remediation therapy is combined with social skills training (e.g., Roder, Mueller, Mueser, & Brenner, 2006) or other psychiatric rehabilitation strategies. Indeed, the future of psychological treatment for schizophrenia may involve an integration of interventions that target emotional support, cognitive problems, and functional recovery as well as psychotic symptoms (Dickerson & Lehman, 2011).

FAMILY THERAPY Patients with schizophrenia who have the support of family members may benefit from **family therapy**. This psychosocial intervention conceptualizes the patient as a member of a family system (Kazarian & Malla, 1992) and thus tailors treatment to the family as a whole. Accordingly, therapy aims for active involvement of each member of the family in the treatment process. The family system is of particular importance because of the current focus on deinstitutionalization; patients with schizophrenia struggle in adjusting to community life, which may include residing with family members. Patients are thus subject to the influence of daily family interactions and to the emotional communication or miscommunication (e.g., expressed emotion) embodied in these interactions. Therapy for the family of a schizophrenia patient may also entail psychoeducation (McFarlane, Dixon, Lukens, & Lucksted, 2003) about the clinical presentation of the disorder, theories pertaining to its causes, and available treatment options. Furthermore, family members may be informed of the potential impact of schizophrenia on the family unit and trained in problem-solving and stress-related coping skills. Each individual family member is asked to make a commitment to supporting the treatment process.

EARLY INTERVENTION The importance of early intervention in schizophrenia has emerged as a central area of research over the past two decades and has received worldwide attention through international organizations and dedicated peer-reviewed journals, such as *Early Intervention in Psychiatry.* Canadian researcher Dr. Jean Addington has devoted much of her career to studying people considered at high risk for developing schizophrenia, as well as to those in the prodromal and first episode phases of the disorder. The

term *prodrome* refers to the period before the appearance of psychotic symptoms when vulnerable adolescents often become withdrawn and suspicious. Those individuals who progress, or "convert," to psychotic disorder are referred to as "first episode" patients because they are experiencing their first episode of intense and unmistakable symptoms. Results from Addington's work reveal that significant cognitive, social, and functional impairments occur at the beginning stages of the disorder and are not simply a product of many years of hospital admissions or social disadvantage (Addington, 2007). In fact, even those young people at high risk for developing psychosis who do not convert to a full-blown psychotic episode continue to function at a level lower than their nonpsychotic peers (Addington et al., 2011). Symptom improvement is probable following early intervention, but cognitive impairments persist and social and functional skills, as well as quality of life, remain deficient when compared to healthy peers. Early intervention is a promising yet extremely challenging aspect of schizophrenia research and practice.

6 BEFORE MOVING ON

Why is it important not to focus exclusively on psychotic symptoms when developing treatments for schizophrenia?

CANADIAN RESEARCH CENTRE

Dr. Christopher Bowie

Clinical psychologist Dr. Christopher Bowie directs a research program at Queen's University in Kingston, Ontario, that investigates neurocognitive abilities and their relationship to everyday functioning in people with schizophrenia. Dr. Bowie's research has both descriptive and treatment aspects. His descriptive work focuses on how impairments in neurocognitive abilities like attention, memory, and executive functions are associated with deficits in the skills necessary for successful community living.

Although many individuals with schizophrenia have a favourable clinical response—a reduction in the symptoms associated with the condition, like hallucinations and delusions—neurocognitive impairments persist, making a return to optimal living difficult. Neurocognitive impairments are present even before the diagnostic symptoms of schizophrenia emerge and are quite severe. Their early presence and their persistence during remission of symptoms make it difficult for those with schizophrenia to attend to, learn, remember, sequence, and generalize the wide range of living skills that are typically acquired during adolescence and early adulthood. When the acquisition of these critical developmental skills is interrupted early in life, and continuously disrupted throughout adulthood by neurocognitive impairments, living independently, working, and socializing remain a challenge for many patients.

Dr. Bowie's work has identified neurocognitive impairments as a key reason why many people with schizophrenia experience difficulties in many domains of daily life functioning. Building on his correlational research, Dr. Bowie and his team are examining the effects of a psychological treatment called *cognitive remediation*. They are comparing theoretically different types of cognitive remediation in vocational rehabilitation programs to examine which types of changes in brain function are associated with improvements in work skills. Additionally, he is using eye-tracking and neurophysiological techniques to examine the underlying changes in brain function associated with cognitive remediation. The long-term goal of his research program is to find new ways to help individuals with schizophrenia restore their functioning and experience an improved quality of life.

SUMMARY

- Schizophrenia is a psychotic disorder that may affect both men and women in late adolescence and early adulthood.
- The disorder is complex and heterogeneous in its clinical presentation, course, and outcome.
- Approximately 50 percent of patients with schizophrenia improve over time and in response to treatment, but few achieve their social and occupational potential, and many require lifelong support and remain at risk for suicide.
- Direct and indirect social and health care costs of schizophrenia approach $7 billion a year in Canada.
- Schizophrenia involves characteristic symptoms that must be present for diagnosis, including hallucinations, delusions, thought and language disorder, bizarre behaviour, and withdrawal.

- The disorder must be associated with a decline in social and occupational functioning.
- Having psychotic symptoms for one day does not mean a person has schizophrenia; these symptoms must persist for at least a month unless successfully treated.
- Mood disorders like depression and other medical and developmental disorders may complicate the diagnosis of schizophrenia and must be ruled out.
- There is no objective test that confirms whether a person has schizophrenia.
- Disorders like schizophrenia may result from many interacting biological and psychosocial influences rather than from a single cause or event.
- Biological and psychosocial processes may increase or decrease the probability that a vulnerable person develops schizophrenia.
- Most theorists argue that both a vulnerability, or diathesis, and environmental stress are required to cause schizophrenia.
- Having a parent with schizophrenia significantly increases the chances that a young person will develop the disorder.
- The influence of parents on the development of schizophrenia in their children is biological and genetic in nature.
- Many genes are implicated in schizophrenia, but their individual effects are very small.
- Epigenetic processes that turn genes on and off may be as important in causing schizophrenia as the genes themselves.
- Slow processing of information, poor coordination, and deficient attention, perception, and learning are characteristic of most people with schizophrenia.
- Abnormalities of the frontal and temporal lobes of the brain are among the most studied features of schizophrenia, but no single brain abnormality occurs in everyone with the disorder.
- Neuroscience research methods provide increasingly accurate and sophisticated information about the structure and physiology of the brain.
- The most frequently implicated neurochemical abnormality in schizophrenia involves the neurotransmitter dopamine.
- Chlorpromazine was the first effective antipsychotic medication used with schizophrenia patients, reducing the severity of positive and, to a lesser degree, negative symptoms.
- A new, second generation of antipsychotic medications provides therapeutic benefits with fewer side effects.
- Antipsychotic medications have little or no effect on the cognitive impairments associated with schizophrenia.
- Significant advances have been made in the application of psychological interventions, like cognitive-behaviour therapy (CBT), family therapy, and cognitive remediation training.
- Cognitive remediation training has potential value for addressing cognitive impairment and may also reduce positive symptoms and improve social functioning in people with schizophrenia.
- Early intervention, whereby medication and psychological therapies are provided before a person develops prolonged psychosis, has become a new and promising focus for clinical researchers.
- Integrated psychosocial and medical therapies offer the most hope for improving the lives of people with schizophrenia.

KEY TERMS

schizophrenia (p. 207)
heterogeneity (p. 207)
prevalence (p. 208)
delusional thinking (p. 209)
madness (p. 209)
lunacy (p. 210)
auditory hallucinations (p. 210)
positive symptoms (p. 210)
psychosis (p. 210)
delusions (p. 210)
hallucinations (p. 210)
thought and speech disorder (p. 210)
catatonic behaviour (p. 210)
negative symptoms (p. 210)
avolition (p. 210)
anhedonia (p. 210)
persecutory delusions (p. 210)
referential delusions (p. 211)

somatic delusions (p. 211)
religious delusions (p. 211)
delusions of grandeur (p. 211)
loosening of associations (p. 211)
affective flattening (p. 211)
waxy flexibility (p. 212)
disease markers (p. 214)
sensitivity (p. 215)
specificity (p. 215)
endophenotype (p. 215)
cognitive marker (p. 215)
eye-tracking (p. 215)
schizophrenogenic (p. 216)
collective unconscious (p. 216)
social drift (p. 216)
diathesis (p. 217)
stress (p. 217)
hypokrisia (p. 217)
cognitive slippage (p. 217)
aversive drift (p. 217)
schizotype (p. 217)
genetic contribution (p. 219)
familiality (p. 219)
penetrance (p. 219)
epigenetic (p. 220)
birth-related complications (p. 220)
high-risk children (p. 221)
expressed emotion (p. 221)
cumulative liability (p. 221)
frontal lobe (p. 221)
meta-analysis (p. 222)
effect size (p. 222)
neuropsychological tests (p. 222)
Wisconsin Card Sorting Test (p. 222)
perseverate (p. 223)
frontal brain deficiency (p. 223)
structural magnetic resonance imaging (MRI) (p. 223)
positron emission tomography (PET) (p. 223)
functional magnetic resonance imaging (fMRI) (p. 223)
left temporal lobe (p. 224)
amygdala (p. 224)
hippocampus (p. 224)
dopamine (p. 225)
neurotransmitters (p. 225)
receptors (p. 225)
ligands (p. 226)
dopamine-blocking drugs (p. 226)
insulin coma (p. 227)
psychosurgery (p. 227)
frontal lobotomy (p. 227)
chlorpromazine (p. 227)
risperidone (p. 228)
olanzapine (p. 228)
social stigma (p. 228)
cognitive-behavioural therapy (p. 228)
social skills training (p. 229)
family therapy (p. 229)