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Schizophrenia Spectrum and Other Psychotic Disorders

Vijay A. Mittal, Andrea Pelletier-Baldelli, Hanan Trotman, Lisa Kestler, Annie Bollini, and Elaine Walker

Schizophrenia is among the most debilitating of mental illnesses. It is typically diagnosed between 20 and 25 years of age, a stage of life when most people gain independence from parents, develop intimate romantic relationships, plan educational pursuits, and begin work or career endeavors (De Lisi, 1992). Because the clinical onset usually occurs during this pivotal time, the illness can have a profound negative impact on the individual's opportunities for attaining social and occupational success, and the consequences can be devastating for the patient's life course, as well as for family members (Addington & Addington, 2005). Further, the illness knows no national boundaries. Across cultures, estimates of the lifetime prevalence of schizophrenia range around 1% (Keith, Regier, & Rae, 1991; Kulhara, & Chakrabarti, 2001; Torrey, 1987; Arajarvi et al., 2005), although there is some research indicating that the rate may be somewhat lower with more stringent measurement criteria (0.4%; Saha Chant, Welham, & McGrath, 2005). Studies also suggest that the prognosis may differ among countries, with better outcomes in developing nations (Kulhara & Chakrabarti, 2001). However, more recent evidence suggest that variation in prognosis may not be that straightforward as there appears to be differences within individual developing nations in course of illness and discrepancies in measurement; it may be that access to treatment is associated with better outcome across countries (Cohen, Patel, Thara, & Gureje, 2008).

The origins of schizophrenia have continued to elude researchers, despite many decades of scientific research. To date, no single factor has been found to characterize all patients with the illness. This holds for potential etiological factors, as well as clinical phenomena. Patients with schizophrenia vary in symptom profiles, developmental histories, family backgrounds, cognitive functions, and even brain morphology and neurochemistry. Although this has led some to express dismay at our chances of ever findings the cause of schizophrenia, there is reason to be optimistic. Research efforts have succeeded in revealing numerous pieces of what is now recognized as a complex puzzle of etiological processes.

Based on findings from various lines of research, the consensus in the field is that: 1) Schizophrenia is a brain disease; 2) its etiology involves the interplay between genetic and environmental factors; 3) multiple developmental pathways eventually lead to disease onset; and 4) brain maturational processes play a role in the etiological process. In this chapter, we provide an overview of the current state of our knowledge about schizophrenia. We begin with a discussion of history and phenomenology of the disorder, and then proceed to a description of some of the key findings which have shed light on the illness.

History and Phenomenology

Written descriptions of patients experiencing psychotic symptoms (i.e. symptoms indicative of an inability to discern what is reality), similar to those of what we now call schizophrenia, have been recorded since antiquity. However, because psychotic symptoms can be a manifestation of a variety of disorders, it is unclear whether schizophrenia, as we view it today, is an ancient or a relatively new phenomenon. In the mid-to-late 19th century, European psychiatrists were investigating the etiology, classification and prognoses of various types of psychosis. The term *psychosis* refers broadly to the presence of psychotic symptoms and may various diagnoses such as schizophrenia-related disorders, together with mood disorders with psychotic features. At that time, the most common cause of psychosis was *tertiary syphilis*, although

researchers were unaware that there was any link between psychosis and syphilis (Kohler & Johnson, 2005). The psychological symptoms of tertiary syphilis frequently overlap with symptoms of what we now call schizophrenia. The cause of syphilis was eventually traced to an infection with the spirochete, *Treponema pallidum*, and antibiotics were found to be effective for prevention and treatment of the disorder. This important discovery served to illustrate how a psychological syndrome can be produced by an infectious agent. It also sensitized researchers to the fact that similar syndromes might be the result of different causes.

Emil Kraepelin (1856–1926) was the medical director of the famous Heidelberg Clinic. He was the first to differentiate schizophrenia, which he referred to as *dementia praecox* (or dementia of the young) from manic-depressive psychosis (Kraepelin, 1913). He also lumped together "hebephrenia," "paranoia," and "catatonia" (previously thought to be distinct disorders), and classified all of them as variants of dementia praecox. He based this classification on their similarities in age of onset and the clinical feature of poor prognosis. Kraepelin did not believe that any one symptom was diagnostic of dementia praecox, but instead focused on the total clinical picture and changes in symptoms over time. If a psychotic patient deteriorated over an extended period of time (months/years), the condition was assumed to be dementia praecox.

Many contemporary mental health professionals continue to expect negative outcomes in those afflicted with schizophrenia, and this expectation infuses the mental health profession with an unfortunate sense of therapeutic nihilism. Yet, while it is true that the majority of patients manifest a chronic course that entails lifelong disability, this bleak scenario is not always inevitable (Carpenter & Buchanan, 1994). The story of Dr. John Nash, professor and mathematician at Princeton, as told in the movie *A Beautiful Mind*, illustrates this point quite well. Dr. Nash was able to function at a very high level in his academic field, despite his struggle with schizophrenia.

Historical and Modern Conceptions of Psychosis Classification The term *schizophrenia* was introduced at the beginning of the 20th century by Eugen Bleuler (1857–1939), a Swiss psychiatrist and the medical director of a mental hospital in Zurich (Howells, 1991, pp. xii, 95). The word is derived from two Greek words: *schizo*, which means to tear or to split, and *phren*, which has several meanings. In ancient times, the word *phren*, meant "the intellect" or "the mind." *Phren* also referred to the lungs and the diaphragm, which were believed to be the seat of emotions. Thus, the word schizophrenia literally means the splitting or tearing of the mind and emotional stability of the patient.

Bleuler classified the symptoms of schizophrenia into fundamental and accessory symptoms. The fundamental symptoms of schizophrenia are often reported in textbooks as the four As, although, in fact, there are six As and one D (Bleuler, 1950). The fundamental symptoms are listed in Box 17.1. According to Bleuler, these symptoms are present in all patients, at all stages of the illness, and are diagnostic of schizophrenia.

Box 17.1 Bleuler's Fundamental Symptoms of Schizophrenia

- Disturbances of **a**ssociation (loose, illogical thought processes).
- Disturbances of **a**ffect (indifference, apathy or inappropriateness).
- **A**mbivalence (conflicting thoughts, emotions or impulses which are present simultaneously or in rapid succession).
- **A**utism (detachment from social life with inner preoccupation).
- **A**bulia (lack of drive or motivation).
- **D**ementia (irreversible change in personality).

Bleuler's "accessory symptoms" of schizophrenia included delusions, hallucinations, movement disturbances, somatic symptoms, and manic and melancholic states. In contrast to fundamental symptoms, he believed that these accessory symptoms were not present in all patients with schizophrenia, and often occurred in other illnesses. For these reasons, the accessory symptoms were not assumed to be as diagnostic of schizophrenia.

Further refinements in the diagnostic criteria for schizophrenia were proposed by Kurt Schneider (1959) in the mid-1900s. Like Bleuler, Kurt Schneider thought that certain "key" symptoms were diagnostic of schizophrenia. In his classification, he referred to these diagnostic symptoms as "first-rank symptoms" (see Box 17.2). He believed that, after medical causes of psychosis were ruled out, one could make the diagnosis of schizophrenia if one or more first-rank symptoms were present. Schneider's descriptions of the symptoms were more detailed and specific than were Bleuler's fundamental symptoms. Subsequent diagnostic criteria for schizophrenia have been heavily influenced by Schneider's approach.

Box 17.2 The Schneiderian "First-Rank Symptoms"

- Thought echoing or audible thoughts (the patient hears his thoughts out loud).
- Thought broadcasting (patient believes that others can hear his thoughts out loud).
- Thought intrusion (patient feel that some of his thought are from outside; that is, not originating in his own mind).
- Thought withdrawal (patient believes that the cause of having lost track of a thought is that someone is taking his thoughts away).
- Somatic hallucinations (unusual, unexplained sensations in one's body).
- Passivity feelings (patient believes that his thoughts, feelings or actions are controlled by another or others).
- Delusional perception (a sudden, fixed, false belief about a particular everyday occurrence or perception.

Following longitudinal research in the 1960s, a German researcher by the name of Gerd Huber laid out a list of symptoms that were evident (through retrospective study) in the early course of illness as well as in the later stages of psychosis (Huber, Gross, Shuttler, & Linz, 1980). These symptoms are termed "basic symptoms" and generally refer to symptoms reported by the patient themselves and include impairment in cognition, perception, motor function, will, initiative, level of energy, and tolerance of stress (Olson & Rosenbaum, 2006).

In subsequent years, investigators began to make a distinction between "positive" and "negative" symptoms of schizophrenia (Harvey & Walker, 1987). The positive symptoms are those that involve an excess of ideas, sensory experiences or behavior. Hallucinations, delusions and bizarre behaviors fall in this category. Most of the first-rank symptoms described by Schneider are also considered to be positive symptoms. Negative symptoms, in contrast, involve a decrease in behavior, such as blunted or flat affect, anhedonia, and lack of motivation. These symptoms were highlighted by Bleuler.

During the middle of the 20th century, different diagnostic criteria for schizophrenia became popular in different parts of the world. The "Kraepelinian" tradition, with its longitudinal requirements for diagnosis, identified patients with poorer long-term prognosis. In contrast, the Bleulerian and Schneiderian diagnostic systems allowed for a wider range of psychotic patients to be diagnosed with schizophrenia. Thus, the patients diagnosed with these two systems tended to have a better prognosis than those diagnosed in the more stringent Kraepelinian tradition. Because of these discrepancies, the use of multiple diagnostic systems had a detrimental effect on research progress; research findings from countries using different diagnostic criteria were not comparable, thus limiting the generalizability of the results.

The next generation of diagnostic systems evolved with the intent of achieving uniformity in diagnostic criteria and improving diagnostic reliability. Among these were the "Feighner" or "St. Louis" diagnostic criteria (Feighner, Robins, & Guze, 1972), and the Research Diagnostic Criteria developed by Robert Spitzer and his colleagues (Spitzer, Endicott, & Robins, 1978). These two approaches to the diagnosis of schizophrenia strongly influenced modern-day diagnostic systems, most notably, the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association, 2013). The DSM is now the most widely used system for diagnosing schizophrenia and other mental disorders.

Although the recent introduction of DSM-5 in May 2013 did not reflect any major departures from the preceding DSM-IV-TR (American Psychiatric Association, 2000), there are several noteworthy minor revisions affecting the diagnosis of schizophrenia. First, schizophrenia is now included with a group of disorders under the category of "Schizophrenia Spectrum and Other Psychotic Disorders," reflecting a shift toward a dimensional understanding of psychosis (Johns & van Os, 2001). As with DSM-IV-TR, there are six criteria (Table 17.1). In contrast to DSM-IV-TR, there are two distinct changes in DSM-5 for criterion A, which highlights specific characteristic symptoms that must be present for a significant amount of time during a 1-month period (or less if treated successfully). First, DSM-5 criterion A states that there must be two characteristic symptoms present from: 1) hallucinations; 2) delusions; 3) disorganized speech (e.g., frequent derailment or incoherence); 4) grossly disorganized or catatonic behavior; and 5) negative symptoms (i.e., affective flattening, alogia, or avolition). This is different, owing to the elimination of allowing for only one of these symptoms to be sufficient if it is bizarre in nature or if it is a Schneiderian first-rank auditory hallucination (e.g., multiple voices conversing with each other) (Tandon et al., 2013). The reason for the change relates to a general consensus in the field that there was poor empirical evidence to support the prior stipulation. Some researchers have indicated that this increased threshold for symptoms may exclude approximately 2% of individuals who held a diagnosis of schizophrenia under DSM-IV-TR (Pagsberg, 2013). Secondly, DSM-5 now requires that at least one of the criterion A symptoms must be a core positive symptom such as hallucinations, delusions, or disorganized speech. The reason for this change is that these three symptom groupings are considered "core positive symptoms" that reflect psychotic pathology (Tandon et al., 2013).

TABLE 17.1
DSM-5 Criteria for Schizophrenia

Criterion	Category	Description
A	Characteristic symptoms	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 should include 1, 2, or 3. 1. Delusions 2. Hallucinations 3. Disorganized speech 4. Grossly disorganized or catatonic behavior 5. Negative symptoms (i.e., diminished emotion expression or avolition)
B	Social/occupational dysfunction	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, are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).
C	Duration	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 and mood disorder exclusion	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	Substance/general medical condition exclusion	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	Relationship to global developmental delay or autism spectrum disorder	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).
	Course specifiers	1. First episode, currently in acute episode 2. First episode, currently in partial remission 3. First episode, currently in full remission 4. Multiple episodes, currently in acute episode 5. Multiple episodes, currently in partial remission 6. Multiple episodes, currently in full remission 7. Continuous 8. Unspecified

There are no changes to criterion B, C, D, or E. Criterion B emphasizes that, in addition to the presence of characteristic symptoms, there must be significant social/occupational dysfunction. Schizophrenia can be diagnosed with DSM-5 when these signs and symptoms of the disorder are present for 6 months (including prodromal and residual phases; Criterion C). Further, significant mood disorders, such as depression or mania, along with schizoaffective disorder must be ruled out to ensure that the symptoms present are not better accounted for by one of these diagnoses (Criterion D). Also, general medical conditions or substance use that might lead to psychotic symptoms must be ruled out (Criterion E). Finally, in DSM-IV-TR, Criterion F stipulated that if a pervasive developmental disorder (PDD) or autistic disorder was present, schizophrenia could only be diagnosed if prominent delusions or hallucinations were present for at least 1 month (or less if successfully treated; DSM-IV-TR, 2000). In DSM-5, this criterion is restated to include "*or other communication disorder of childhood onset*" along with autism to acknowledge that there are additional disorders that may warrant diagnostic differentiation (Dyck, Piek, & Patrick, 2011; Tandon et al., 2013). In sum, the changes to the criterion (A and F specifically) appear to be minor and justified by existing evidence, will not significantly affect those individuals already carrying a diagnosis of schizophrenia, and will likely allow for improved diagnostic clarification.

Notably, the four subtypes of schizophrenia described in DSM-IV-TR (paranoid, disorganized, catatonic and undifferentiated) are no longer included in DSM-5, owing to minimal diagnostic stability and utility, as well as poor reliability and validity (Tandon et al., 2013). In place of these subtypes, a dimensional rating of severity of core symptoms is included in Section III, a section of the manual that includes tools to enhance diagnosis. The schizophrenia workgroup had strongly recommended including this dimensional approach in the primary text section but

this decision was overturned at the last minute because the American Psychiatric Association (APA) was concerned that this would hamper communication between providers and insurance companies (Barch et al., 2013). In any case, the inclusion of this new dimensional approach in DSM-5 highlights the heterogeneous presentation of schizophrenia and in theory, negates the necessity of subtypes while providing the possibility for increased diagnostic description for more effective communication between providers (Pagsberg, 2013).

There are also eight course specifiers for schizophrenia in DSM-5 that define the acute and longitudinal nature of the illness. These specifiers indicate whether the episode being assessed is the first episode or one of multiple episodes, along with coding whether the episode is active (currently in acute episode) or in full or partial remission. Finally, there are two course specifiers that allow for some ambiguity through labeling the episodes as continuous (i.e. the episodes are too continuous to determine a specific course of symptoms) and unspecified (i.e. the information needed to clarify course of symptoms is lacking). In addition to several other considerations, the purpose of these changes was to reduce comorbidity and the incidence of the "not otherwise specified" diagnoses and to improve diagnostic communication between healthcare providers. It remains to be seen whether comorbidity and diagnostic ambiguity will lessen and communication improve through these changes; however, the specifiers do appear to add some specificity to course of illness description that was absent in previous diagnostic manuals.

Also new in Section III of DSM-5 is the inclusion of *attenuated psychosis syndrome* (APS). This category identifies individuals who do not meet full criteria for schizophrenia, but who exhibit attenuated (less intense or severe) characteristic symptoms and intact reality testing. These individuals are at heightened risk of developing a psychosis spectrum disorder—as many as 30% will go on to develop a psychosis in a 2-year period (Cannon et al., 2008). The decision to include the new diagnosis accompanied a fierce debate in the period leading up to publication. Although expert consensus for the diagnosis is still evolving, the impetus for including APS in DSM-5 arose from accumulating evidence that high-risk patients are currently ill and at elevated risk for more serious mental illness (Cannon et al., 2008), the criteria for a risk state can be assessed with reliability and validity (in a research setting), and no DSM-IV diagnosis accurately captured the current illness/future risk (Addington et al., 2007; Yung et al., 2007). The proponents argued that providing a DSM-5 diagnosis could minimize potential harm to patients and families and could improve general provider education (Woods et al., 2010). Those who argued against the new label suggested that inclusion was premature because of a lack of information from community-based trials and significant concern about stigma (Shrivastava et al., 2011). Opponents also questioned the clinical validity of the syndrome because APS is predictive of a number of disorders outside schizophrenia (e.g., affective psychoses) and therefore, the label is in a non-specific initial stage. These critics also noted that because a primary focus relates to risk for future illness, a high rate of false positives (i.e., those who do not transition to psychosis) is ethically problematic as it exposes a disproportionate number of youth to unnecessary medications and stigma (Corcoran, First & Cornblatt, 2010). The ultimate decision to place APS in the research section of DSM-5 speaks to the valid points on both sides of this debate, and to the complex and delicate issues accompanying the diagnosis.

Several other diagnoses under the 'schizophrenia spectrum and other psychotic disorders' group are worth noting. The first is *schizotypal personality disorder* (SPD), which now falls both under this grouping, as well as under personality disorders. The diagnostic criteria for SPD includes social anxiety or withdrawal, affective abnormalities, eccentric behavior, unusual ideas (e.g., persistent belief in extrasensory perception/phenomena, aliens), and unusual sensory experiences (e.g., repeated experiences with confusing noises with peoples' voices, or seeing objects move). Although the individual's unusual ideas and perceptions are not severe or persistent enough to meet criteria for delusions or hallucinations, they are recurring and atypical of the person's cultural context. An extensive body of research demonstrates genetic and developmental links between schizophrenia and SPD. The genetic link between SPD and schizophrenia has been documented in twin and family history studies (Kendler, McGuire, Gruenberg, & Walsh, 1995; Kendler, Neale, & Walsh, 1995; Raine & Mednick, 1995). The developmental transition from schizotypal signs to schizophrenia in young adulthood has been followed in several recent longitudinal studies, with researchers reporting that 20–40% of schizotypal youth eventually develop a schizophrenia spectrum disorder (Cannon et al., 2008; Miller et al., 2002; Yung et al., 1998). The inclusion of schizotypal personality disorder in this grouping again illustrates the shift towards conceptualizing psychosis on a dimensional continuum.

An additional category, *schizophreniform disorder*, is for individuals whose symptoms do not meet the 6-month criterion. This diagnosis is frequently made as a prelude to the diagnosis of schizophrenia, when the patient presents for treatment early in the course of the disorder. Some individuals who fall into this category, however, will recover completely and not suffer further episodes of psychosis.

It is important to emphasize that, despite advances in diagnosis, the diagnostic boundaries of schizophrenia are still quite unclear (Wolff, 1991). Moreover, the boundaries between schizophrenia and mood disorders are sometimes obscure. Many individuals who meet criteria for schizophrenia show marked signs of depression or manic tendencies. These symptoms are sometimes present before the onset of schizophrenia, and frequently occur in combination with marked psychotic symptoms. As a result, the DSM-5 includes a diagnostic category called *schizoaffective disorder*. This disorder can be conceived

of, conceptually, as a hybrid between the mood disorders (bipolar disorder or major depression with psychotic features) and schizophrenia. The two subtypes of schizoaffective disorder are the depressive subtype (i.e., if the mood disturbance includes only depressive episodes) and the bipolar subtype (i.e., where the symptoms of the disorder have included either a manic or a mixed episode). Interestingly, the prognosis for patients with schizoaffective disorder is, on average, somewhere between that of schizophrenia and the mood disorders. Of note, DSM-5 changes affecting schizoaffective disorder include diagnosis based on consideration of the life course rather than just the current episode, such that mood disorder must be present for the majority of the total disorder duration after criterion A has been met (American Psychiatric Association, 2013).

Cognitive and Social Processes Deficits in Schizophrenia

Among the most well-established aspects of schizophrenia are the cognitive impairments that accompany the illness. In fact, some experts argued that cognitive impairment should have been added as a characteristic symptom in the DSM-5 (Keefe & Fenton, 2007); however, the DSM-5 Task Force decided against making this recommendation because of its lack of diagnostic specificity. Patients with schizophrenia manifest performance deficits on a broad range of cognitive tasks, from simple to complex (Green, Kern, Braff, & Mintz, 2000; Bozikas, Kosmidis, Kiosseoglou, & Karavatos, 2006). One of the most basic is the deficit in the very earliest stages of visual information processing. Using a laboratory procedure called backward masking, researchers have shown that compared with both healthy individuals and psychiatric controls, patients with schizophrenia are slower in the initial processing of stimuli (Green, Nuechterlein, Breitmeyer, & Mintz, 1999, 2006). One interesting finding in patients with schizophrenia relates to perceptual functioning. Individuals with schizophrenia tend not to be susceptible to optical illusions such as perceiving two-dimensional objects in three-dimensional form, and these perceptual impairments can actually produce superior performance on certain tasks (Keane, Silverstein, Wang, & Papathomas, 2013). In general, research suggests that patients with schizophrenia show deficits in attention/vigilance, context processing, working memory, episodic memory, verbal learning, visual learning, and reasoning and problem solving (Nuechterlein et al., 2004; Barch & Ceasar, 2012). Of note, there is some evidence that nicotine is beneficial to such cognitive impairments; there is ongoing work evaluating its effectiveness in clinical trials (Hong et al., 2011; Lieberman et al., 2013).

There are also deficits in thinking about social phenomena. Studies of social-cognitive abilities in schizophrenia patients have consistently shown that patients are impaired in their ability to comprehend and solve social problems, processing of emotions, social perception, attribution of events, and theory of mind (the ability to perceive the judgments, beliefs, intentions, and emotions of others; Green & Horan, 2010; Hooley, 2010; Penn, Corrigan, Bentall, Racenstein, & Newman, 1997; Meherwan Mehta et al., 2013). Social-cognitive imaging studies consistently point to abnormalities in brain regions and circuitry associated with social processing, adding to the evidence showing that social-cognitive impairment is a hallmark feature of schizophrenia. Deficits in social cognition may be partially due to limitations in more basic cognitive processes, such as memory and reasoning (Kring & Elis, 2013). However, basic cognitive impairments do not account completely for the more pervasive and persistent social-cognitive dysfunction observed in schizophrenia, and there is increasing evidence to support the idea that social cognition is a separate construct (Meherwan Mehta et al., 2013). For example, imaging studies show that there is something unique in brain activation when an individual is involved in a social versus strictly cognitive task, along with other research that finds social-cognitive and cognitive tasks often load on different domains when evaluated together using a statistical technique called factor analysis (Billike and Abowitz, 2013).

One of the diagnostic criteria for schizophrenia is blunted or inappropriate affect. It is not surprising therefore, that patients show abnormalities in the expression of emotion in both their faces and verbal communications. These abnormalities include less positive and more negative emotion, as well as emotional expressions that seem inconsistent with the social context (termed inappropriate affect; Brozgold et al., 1998; Tremeau et al., 2005). Further, patients with schizophrenia are less accurate than unaffected comparison subjects in their ability to label facial expressions of emotion, with a particular difficulty in labeling fear and sadness (Penn et al., 2000; Walker, E., 1981; Martin, Baudouin, Tiberghien, & Franck, 2005; Bigelow et al., 2006; Amminger et al., 2012). Numerous studies have examined the link between social-cognitive impairments, such as emotional processing and social functioning, indicating a strong relationship between poor social-cognitive ability and social difficulties (Salva et al., 2013). Specifically, research indicates that social cognition may be more closely tied to functioning than other cognitive domains, suggesting that social-cognition may be especially informative for understanding etiology and developing treatment (Fett et al., 2011).

Research Domain Criteria Initiative In 2009, the National Institute of Mental Health (one of the primary funding sources for research on schizophrenia) created a working group to set in motion efforts to develop new ways of classifying psychopathology based on dimensions of observable behavior and neurobiological measures. The aim of this effort is to acknowledge the need for a new approach to research aimed at cutting across diagnostic labels to create improved classification of mental

disorders through understanding underlying dimensions of functioning. Further, a focus of this initiative is to integrate multiple levels of analysis including genes, behavior, and neurobiology with the hope of translating basic research into improved understanding of psychopathology and better targeted treatment. While DSM-5 is purely a diagnostic tool, the Research Domain Criteria Initiative provides an alternate framework for research and has the potential to redefine mental disorders in future versions of the DSM.

The Origins of Schizophrenia

Biological Theories Kraepelin, Bleuler, and other early writers on schizophrenia did not offer specific theories about the origins of schizophrenia. They did suggest, however, that there might be a biological basis for at least some cases of the illness. Likewise, contemporary ideas about the origins of schizophrenia focus on biological vulnerabilities that are assumed to be present in early development. Researchers have identified two sources of constitutional vulnerability: genetic factors and environmental factors (e.g., prenatal or obstetric complications, traumatic brain injury). Both appear to have implications for prenatal and postnatal brain development, which is a focus of our understanding of the development of schizophrenia.

The Genetics of Schizophrenia One of the most well-established findings in schizophrenia research is that a vulnerability to the illness can be inherited (Gottesman, 1991). Behavior genetic studies utilizing twin, adoption and family history methods have all yielded evidence that the risk for schizophrenia is elevated in individuals who have a biological relative with the disorder; the closer the level of genetic relatedness, the greater the likelihood the relative will also suffer from schizophrenia.

In a review of family, twin, and adoption studies conducted from 1916 to 1989, Irving Gottesman (1991) outlined the compelling evidence for the role of genetic factors in schizophrenia. Monozygotic twins, who essentially share 100% of their genes, have the highest concordance rate for schizophrenia. Among monozygotic co-twins of patients with schizophrenia, 25–50% will develop the illness. Dizygotic twins and other siblings share, on average, only about half of their genes. About 10–15% of the dizygotic co-twins of patients are also diagnosed with the illness. Further, as genetic relatedness of the relative to the patient becomes more distant, such as from first-degree (parents and siblings) to second-degree relatives (grandparents, half siblings, aunts, and uncles), the relative's lifetime risk for schizophrenia is reduced.

Adoption studies have provided evidence that the tendency for schizophrenia to run in families is primarily due to genetic factors, rather than the environmental stressors related to growing up in close proximity to a mentally ill family member. In a seminal adoption study, Heston (1966) examined the rates of schizophrenia in adoptees with and without a biological parent who was diagnosed with the illness. He found higher rates of schizophrenia, and other mental illnesses, in the biological offspring of parents with schizophrenia, when compared with adoptees with no mental illness in biological parents. Similarly, in a Danish sample, Kety (1988) examined the rates of mental illness in the relatives of adoptees with and without schizophrenia. He found that the biological relatives of adoptees who suffered from schizophrenia had a significantly higher rate of the disorder than the adoptive relatives who reared them. Also, the rate of schizophrenia in the biological relatives of adoptees with schizophrenia was higher than in the relatives (biological or adoptive) of healthy adoptees. These adoption studies provide ample evidence for a significant genetic component in the etiology of schizophrenia.

Findings from an adoption study in Finland indicate that genetic influences often act in concert with environmental factors. Tienari, Wynne, Moring, and Lahti (1994) found that the rate of psychosis and other severe disorders was significantly higher in adoptees who had biological mothers with schizophrenia than in the matched control adoptees who had no history of having a first-degree relative with psychosis. However, the difference between the groups was only detected in adoptive families that were rated as dysfunctional. The genetic vulnerability was mainly expressed in association with a disruptive adoptive environment, and was not detected in adoptees reared in a healthy, possibly protective, family environment. These findings, which highlight a genetic vulnerability interacting with environmental events, are consistent with the prevailing diathesis-stress models of etiology. Taken together, the findings from behavioral genetic studies of schizophrenia lead to the conclusion that the disorder involves multiple genes, rather than a single gene (Gottesman, 1991; Van Winkel et al., 2010).

Consistent with this assumption, attempts to identify a genetic locus that accounts for a significant proportion of cases of schizophrenia have not met with success. Instead, researchers using molecular genetic techniques have identified numerous genes that may account for a small proportion of cases. In the past decade, linkage studies using genome-wide association scans have evaluated over 1,000 genes for schizophrenia (Gejman, Sanders, & Kendler, 2011). Association studies compare variations in specific gene sequences between individuals with and without schizophrenia. Variants found with significantly different frequency among those with schizophrenia are considered to confer susceptibility to the disease. Results from association studies generally have very small effect sizes, owing to the large number of gene variants that can potentially be evaluated; thus, while replication is critical, efforts to do so have met with limited success (Gejman et al., 2011). However, through combining data from multiple studies, results have uncovered a number of notable common polymorphisms (variations in DNA sequence, such

as single nucleotide polymorphisms involving the alteration in a single nucleotide of the DNA sequence) and copy number variants (variations in DNA structure involving the number of copies of a section of DNA within an individual's genotype; Van Winkel et al., 2010; Insel, 2010; Gejman et al., 2011). Findings highlight the heterogeneity of schizophrenia in that thousands of polymorphisms and multiple rare copy number variants (larger alterations in the DNA structure occurring relatively rarely in the population) may underlie the disorder, suggesting that the risk accounted for by each individual variant is small (Purcell et al., 2009; van Winkel et al., 2010). Despite the large number of genetic variants involved, research postulates that approximately 32% of the underlying contribution to schizophrenia may be explained by such common polymorphisms (Purcell et al., 2009; Ripke et al., 2013).

Using quantitative genetic techniques with large twin samples, researchers have shown that there is significant overlap in the genes that contribute to schizophrenia, schizoaffective disorder, bipolar disorder, and other neurodevelopmental disorders such as autism (Cardno, Rijsdijk, Sham, Murray, & McGuffin, 2002; Fanous & Kendler, 2005; van Winkel et al., 2010). Based on these and other findings, many experts have concluded that genetic vulnerability does not conform to the diagnostic boundaries listed in DSM and other taxonomies (e.g., Boks, Leask, Vermunt, & Kahn, 2007; Pelletier & Mittal, 2012). Rather, it appears that there is a genetic vulnerability to psychosis in general, and that the expression of this vulnerability can take the form of schizophrenia or an affective psychosis, depending on other genetic and acquired risk factors. Clearly, more research is needed to understand the specificity for genetic liability for schizophrenia and mood disorders.

As mentioned above, we now know that the environment begins to have an impact before birth; prenatal events are linked with risk for schizophrenia, and some of these events are discussed below. Thus, in order to index environmental events that contribute to non-genetic constitutional vulnerability, we must include both the prenatal and postnatal periods. At this point, however, researchers are not in a position to estimate the relative magnitude of the inherited and environmental contributors to the etiology of schizophrenia. Moreover, we do not yet know whether genetic vulnerability is present in all cases of schizophrenia. Some cases of the illness may be solely attributable to environmental risk factors.

Neurotransmitters The idea that schizophrenia involves an abnormality in the brain first began with a focus on neurotransmission. Initial neurotransmitter theories focused on epinephrine and norepinephrine. Subsequent approaches have hypothesized that serotonin, glutamate and/or gamma-aminobutyric acid (GABA) abnormalities are involved in schizophrenia. But, compared with other neurotransmitters, dopamine has played a more enduring role in theorizing about the biochemical basis of schizophrenia. In this section, we review the major neurotransmitter theories of schizophrenia, with an emphasis on dopamine.

In the early 1950s, investigators began to suspect that dopamine might be playing a central role in schizophrenia. Dopamine is widely distributed in the brain and is one of the neurotransmitters that enables communication in the circuits that link subcortical with cortical brain regions (Jentsch, Roth, & Taylor, 2000). Since the 1950s, support for this idea has waxed and waned. In the past decade, however, there has been a resurgence of interest in dopamine, largely because research findings have offered a new perspective.

The initial support for the role of dopamine in schizophrenia was based on two indirect pieces of evidence (Carlsson, 1988): 1) Drugs that reduce dopamine activity also serve to diminish psychotic symptoms; and 2) drugs that heighten dopamine activity exacerbate or trigger psychotic episodes. It was eventually shown that standard antipsychotic drugs had their effect by blocking dopamine receptors, especially the "D2" subtype that is prevalent in subcortical regions of the brain. The newer antipsychotic drugs, or "atypical" antipsychotics, have the advantage of causing fewer motor side effects. Nonetheless, they also act on the dopamine system by blocking various subtypes of dopamine receptors.

The relationship between dopamine activity and psychotic symptoms can be demonstrated by studies examining compounds, such as levodopa, that are used to treat Parkinson's disease by increasing dopamine transmission. For example, motor abnormalities associated with Parkinson's disease (i.e., hypokinesias; slow jerking movements, rigidity) are related to low levels of dopamine characteristic of the disease. However, patients with Parkinson's disease, who are being treated with dopamine agonists (i.e., levodopa-induced elevated striatal dopamine activity) show drug-induced dyskinesias (i.e., involuntary bodily movements such as writhing or jerking; Hoff, Plas, Wagemans, & van Hilten, 2001), and in extreme cases, psychotic symptoms (Papapetropoulos & Mash, 2005). In a similar vein, other amphetamines such cocaine, increase dopamine activity and can cause both hyperkinesias and psychotic symptoms (Weiner, Rabinstein, Levin, Weiner, & Shulman, 2001). The interplay between dopamine activity and movement has also been seen in research examining genetics and drug responsivity in schizophrenia. For example, schizophrenia patients with the type *3 or *4 alleles of the CYP2D6 gene related to poor metabolization of neuroleptic drugs show a heightened rate of dyskinesias (Ellingrod, Schultz, & Arndt, 2002).

Early studies of dopamine in schizophrenia sought to determine whether there was evidence of excess neurotransmitter in patients with schizophrenia. But concentrations of dopamine and its metabolites were generally found not to be elevated in body fluids from patients with schizophrenia. When investigators examined dopamine receptors, however, there was some evidence of increased

densities. Both postmortem and functional magnetic resonance imaging studies of patients' brains yielded evidence that the number of dopamine D2 receptors tends to be greater in patients than normal controls (Kestler, Walker, & Vega, 2001). Controversy has surrounded this literature, because antipsychotic drugs can change dopamine receptor density. Nonetheless, even studies of never-medicated patients with schizophrenia have shown elevations in dopamine receptors (Kestler et al., 2001). Thus, the first version of the dopamine hypothesis was formed, which focused on hyperdomapinergic (increased levels of dopamine) activity in the brain based on noted increased transmission of dopamine and the blocking of receptors to treat psychosis; this hypothesis was further refined in the 1990s to highlight hyperdopaminergic activity in the subcortical regions of the brain and hypoactiviation in the prefrontal cortex (Howes & Kapur, 2009).

The role of dopamine in schizophrenia has been further clarified following research showing additional abnormalities in dopamine transmission. For example, dopamine synthesis and release may be more pronounced in the brains of people with schizophrenia than among unaffected individuals (Lindström et al., 1999). When patients with schizophrenia and normal controls are given amphetamine, a drug that enhances dopamine release, the patients show more augmented dopamine release (Abi-Dargham et al., 1998; Soeares & Innis, 1999). Further, there are a number of replicated studies showing elevated presynaptic dopamine availability in patients with psychosis (Howes & Kapur, 2009). In concordance with these results, more recent evidence suggests that the primary dopamine activity abnormalities for schizophrenia exists in the three areas involving presynapse, synapse and release of dopamine, rather than in the dopamine receptors themselves (Howes et al., 2012). At present, antipsychotic medications do not target these areas, and there is some suggestion to emphasize presynaptic synthesis and release in treatment efforts (Howes et al., 2012).

Glutamate, an excitatory neurotransmitter, also may play an important role in the neurochemistry of schizophrenia. Glutamatergic neurons are part of the pathways that connect the hippocampus, prefrontal cortex, and thalamus, all regions that have been implicated in schizophrenia. There is evidence of diminished activity at glutamatergic receptors among patients with schizophrenia in these brain regions (Carlsson, Hansson, Waters, & Carlsson, 1999; Coyle, 2006; Ghose, Gleason, Potts, Lewis-Amezcua, & Tamminga, 2009; Marsman et al., 2013). One of the chief receptors for glutamate in the brain is the N-methyl-D-aspartic acid (NMDA) subtype of receptor. Blocking NMDA receptors produces the symptomatic manifestations of schizophrenia in normal subjects, including negative symptoms and cognitive impairments. For example, administration of NMDA receptor antagonists, such as phencyclidine and ketamine, induces a broad range of schizophrenic-like symptomatology in humans, and these findings have contributed to a hypoglutamatergic (decreased levels of glutamate in the brain) hypothesis of schizophrenia (Coyle, 2006; Marsman et al., 2013). Conversely, drugs that indirectly enhance NMDA receptor function can reduce negative symptoms and improve cognitive functioning in schizophrenia patients. It is important to note that the idea of dysfunction of glutamatergic transmission is not inconsistent with the dopamine hypothesis of schizophrenia, because there are reciprocal connections between forebrain dopamine projections and systems that use glutamate (Grace, 2010). Thus, dysregulation of one system would be expected to alter neurotransmission in the other (Stone, Morrison, & Pilowsky, 2007). Furthermore, the progressive deterioration of brain tissue seen in schizophrenia may be tied to the dysfunction of the NMDA receptors and the glutamatergic system (Marsman et al., 2013).

There also is evidence of abnormalities in GABA neurotransmission in the dorsolateral prefrontal cortex (Lewis & Hashimoto, 2007; Lewis et al., 2012). Although the implications of GABA alterations remains unclear (Taylor, Demeter, Luan Phan, Tso, & Welsh, 2013), disruptions in GABA, an inhibitory neurotransmitter, may underlie the reduced capacity for working memory in schizophrenia. Current theories about the role of GABA in schizophrenia assume that it is important because cortical processes require an optimal balance between GABA inhibition and glutamatergic excitation (Costa et al., 2004). In addition to work highlighting the connection between GABA and cognition, recent research has identified potential clinical relevance of GABA. For example, the blockage of GABA receptor activity can create psychotic symptoms in individuals with schizophrenia who are not actively psychotic (Ahn, Gil, Seibyl, Sewell, & D'Souza, 2011). Furthermore, current evidence suggests that GABA receptors are linked with negative affect in schizophrenia (Taylor et al., 2013).

The true picture of the neurochemical abnormalities in schizophrenia may be more complex than we would like to assume. All neurotransmitter systems interact in intricate ways at multiple levels in the brain's circuitry (Carlsson et al., 2001). Consequently, an alteration in the synthesis, reuptake or receptor density, and/or affinity for any one of the neurotransmitter systems would be expected to have implications for one or more of the other neurotransmitter systems. Further, because neural circuits involve multiple segments that rely on different transmitters, it is easy to imagine how an abnormality in even one specific subgroup of receptors could result in the dysfunction of all the brain regions linked by a particular brain circuit.

Abnormalities in Brain Structure The first reports of abnormal brain structure in individuals with schizophrenia were based on computerized axial tomography (CAT), and showed that affected individuals had enlarged brain ventricles, especially increased volume of the lateral ventricles (Dennert & Andreasen, 1983). However, these signs

were viewed as non-specific because enlarged ventricles could reflect wide spread brain matter abnormalities (i.e., smaller volume is reflected in larger ventricles). As new techniques for brain scanning were developed, these findings were replicated, and additional abnormalities were detected (Henn & Braus, 1999). Magnetic resonance imaging, a technique capable of providing significantly greater detail, revealed decreased frontal, temporal and whole brain volume among people with schizophrenia (Lawrie & Abukmeil, 1998; Tanskanen et al., 2010). More fine-grained analyses demonstrated reductions in the size of the anterior cingulate, amygdala, thalamus, insula, and hippocampus (Shepard et al., 2012). Diffusion tensor imaging (DTI) has allowed investigators to examine neuronal connections and white matter tracts in the brain and has shown widespread pathology in multiple tracts. White matter integrity refers to the ability of water molecules to diffuse along the axon in one direction and thus indicates increased fiber integrity and level of myelination. Deficient white matter integrity may be particularly present in the fronto-temporal areas of the brain (Ellison-Wright and Bullmore, 2009). Furthermore, recent evidence suggests that white matter integrity may be related to negative symptoms of schizophrenia (Nakamura et al., 2012).

Current neurodevelopmental theory of schizophrenia postulates that there may be deficient myelination and interneuron activity in the brain along with excessive pruning of excitatory synapses (i.e. overstepping the normal maturational process of removing synapses no longer in use) and that the aggregate impact of these abnormalities may account for the progressive decrease in gray matter volume seen in schizophrenia (Insel, 2010). Furthermore, the deficient myelination may be related to abnormal connectivity within the brain, emphasizing the need to further study brain circuitry using methods such as DTI.

There is also a wealth of evidence to suggest that irregularities in neural development during the adolescent period (immediately before the mean age of onset) contribute to the abnormalities of structural and connective tissue observed in adults with schizophrenia. Although few longitudinal studies of high-risk individuals (prospective designs) have been conducted, results suggest a developmental pattern of declining gray matter structures in left inferior fontal, medial temporal, cerebral and cingulate regions (Job, Whalley, Johnstone, & Lawrie, 2005; Pantelis et al., 2007). Further, a recent meta-analysis of gray matter in high-risk patients who were not taking antipsychotics revealed decreased gray matter in the temporal and limbic prefrontal cortex along with reductions in temporal, anterior cingulate, cerebellar, and insular regions being associated with psychosis onset in first-episode patients (Fusar-Poli, Radua, McGuire, & Borgwardt, 2012). In regards to white matter, the results of high-risk research is very heterogeneous, noting numerous tracts and various lobes exhibiting white matter abnormalities. Researchers have observed DTI evidence that patients failed to show a normal pattern of increasing white matter integrity with age (Karlsgodt et al., 2009; Carletti et al., 2012) and findings indicate declining white matter integrity coinciding with progression to psychosis (von Hohenberg et al., 2013). Specifically, multiple studies have highlighted reduced white matter integrity in the superior longitudinal fasciculus, together with connections involving the frontal, fronto-temporal and fronto-limbic regions (Karlsgodt et al., 2009; Bloemen et al., 2010; Carletti, et al, 2012; Samartzis, Dima, Fusar-Poli, & Kyriakopoulos, 2013; von Hohenberg et al., 2013; Mittal et al., 2013; Dean et al., 2013; Bernard et al., 2014). Taken together, this accumulating evidence points to a prominent role of abnormal adolescent neurodevelopment and conductivity in the pathogenesis of schizophrenia and suggests that many of the noted structural and connective deficits may have been present prior to the formal onset of illness.

Despite the plethora of research findings indicating the presence of abnormalities in the brains of patients with schizophrenia, no specific abnormality has yet been shown to be definitely pathognomonic. In other words, there is no evidence that a specific morphological abnormality is unique to schizophrenia or characterizes all schizophrenia patients. The structural brain abnormalities observed in schizophrenia are, therefore, gross manifestations of the occurrence of a deviation in neurodevelopment that has implications for the functioning of neurocircuitry.

Psychosocial and Environmental Theories In the early part of the 20th century, psychosocial theories of schizophrenia dominated the literature. For example, Sigmund Freud, the father of psychoanalysis, believed that psychological processes resulted in the development of psychotic symptoms (Howells, 1991). In 1948, Frieda Fromm-Reichmann proposed a theory of schizophrenia which postulated that the disorder arose in response to rearing by a 'schizophrenogenic mother' (Fromm-Reichmann, 1948). Although this hypothesis has fallen into disfavor because of a lack of support from empirical research, it caused considerable suffering for families. Subsequently, family interaction models of the etiology of schizophrenia were offered by various theorists (Howells, 1991). Although these early psychosocial theories contributed relatively little to our understanding of the etiology of schizophrenia, they did highlight the importance of considering the role of the family in relapse prevention and recovery for the patient. There has also been considerable focus on other types of environmental stressors involving prenatal and perinatal factors.

Prenatal and Perinatal Factors There is extensive evidence that obstetric complications have an adverse impact on the developing fetal brain, and may contribute to vulnerability for schizophrenia. Birth cohort studies have

shown that patients with schizophrenia are more likely to have a history of exposure to obstetric complications (Brown & Derkits, 2010; Buka, Tsuang & Lipsitt, 1993; Dalman, Allebeck, Cullberg, Grunewald, & Koester, 1999; Forsyth et al., 2013; Takagai et al., 2006). Included among these are prenatal conditions, such as toxemia and preeclampsia, and labor and delivery complications. A meta-analysis of the literature on obstetric complications by Cannon, Jones, and Murray (2002) concluded that, among the different types of obstetric complication, complications of pregnancy (bleeding, preeclampsia, diabetes, and rhesus factor incompatibility) were the most strongly linked with later schizophrenia, followed by abnormal fetal growth and development and complications of delivery. In the National Collaborative Perinatal Project, which involved over 9,000 children followed from birth through adulthood, the odds of developing adult onset schizophrenia increased linearly with an increasing number of hypoxia-related complications (resulting from lack of oxygen at birth; Cannon, 1998; Zornberg, Buka, & Tsuang, 2000).

Another prenatal event that has been linked with increased risk for schizophrenia is maternal viral infection. The risk rate for schizophrenia is elevated for individuals born shortly after an influenza epidemic (Barr, Mednick, & Munk-Jorgensen, 1990; Brown et al., 2004; Limosin, Rouillon, Payen, Cohen, & Strub, 2003; Murray, Jones, O'Callaghan, & Takei, 1992), or after being prenatally exposed to rubella (Brown, Cohen, Harkavy-Friedman, & Babulas, 2001). For example, research suggests that there may be a threefold increase in risk for schizophrenia if a fetus is exposed to influenza in the first half of gestation and sevenfold increase if exposed in the first trimester (Brown & Derkits, 2010). The findings from research on prenatal maternal infection might be connected to the "season-of-birth" effect in schizophrenia. A meta-analysis has shown that a disproportionate number of patients with schizophrenia are born during the winter months (Davies, Welham, Chant, Torrey, & McGrath, 2003). This timing may reflect seasonal exposure to viral infections, which are most common in late fall and early winter. Thus, the fetus would have been exposed to the infection during the second trimester. The second trimester is an important time for brain development, and disruptions during this stage may lead to developmental abnormalities.

Studies of rodents and non-human primates have shown that prenatal maternal stress can interfere with fetal brain development, and is associated with elevated glucocorticoid release and hippocampal abnormalities in the offspring (Charil, Laplante, Vaillancourt, & King, 2010; Coe et al., 2003). Along the same lines, in humans there is evidence that stressful events during pregnancy are associated with greater risk for schizophrenia and other psychiatric disorders in adult offspring. Researchers have linked the incidence of schizophrenia to various maternal stressors during pregnancy, including bereavement (Huttunen, 1989), famine (Susser & Lin, 1992; St Clair et al., 2005), military invasion (van Os & Selten, 1998), war (Malaspina et al., 2008), flood (Selten, Graaf, van Duursen, Gispen-de Wied, & Kahn, 1999) and earthquake (Watson, Mednick, Huttunen, & Wang, 1999). It is likely that prenatal stress triggers the release of maternal stress hormones, which have been found to disturb fetal neurodevelopment and subsequent functioning of the hypothalamic–pituitary–adrenal (HPA) axis, which, in turn influences behavior and cognition (Seckl & Holmes, 2007). In addition, maternal stress may affect maternal proinflammatory cytokines, which have been associated with increased risk of offspring with schizophrenia (Brown & Derkits, 2010).

One of the chief questions confronting researchers is whether obstetric complications act independently to increase risk for schizophrenia or have their effect in conjunction with a genetic vulnerability (Mittal, Ellman, & Cannon, 2008). One possibility is that the genetic vulnerability for schizophrenia involves an increased sensitivity to prenatal factors that interfere with fetal neurodevelopment (Cannon, 1998; Preti, 2005; Walshe et al., 2005). It is also plausible that obstetric events act independently of genetic vulnerabilities, although such effects would likely entail complex interactions among factors (Susser, Brown, & Gorman, 1999). For example, to produce the neurodevelopmental abnormalities that confer risk for schizophrenia, it may be necessary for a specific obstetric complication to occur during a critical period of cellular migration and/or in conjunction with other factors such as maternal fever or immune response. Research shows evidence that the presence of serious obstetric complications may interact with certain genes, those that are regulated by hypoxia or involved in neurovascular function, to increase risk for schizophrenia (Nicodemus et al., 2008). More recently, there is some evidence to suggest that the former hypothesis is true—that genetic vulnerability heightens susceptibility for the development of brain abnormalities following obstetric complications (Forsyth et al., 2013).

Course and Prognosis

Assuming that genetic and obstetrical factors confer the vulnerability for schizophrenia, the diathesis must be present at birth. Yet, schizophrenia is typically diagnosed in late adolescence or early adulthood, with the average age of diagnosis in males about 4 years earlier than for females (Riecher-Rossler & Hafner, 2000). This raises intriguing questions about the developmental course prior to the clinical onset.

Premorbid Development There is compelling evidence that there are signs of schizophrenia long before the illness is diagnosed. Most of these signs are subtle and do not reach the severity of clinical disorder. Nonetheless, when compared with children with healthy adult outcomes, children who later develop schizophrenia manifest deficits in multiple domains. In some of these domains, the deficits are apparent as early as infancy.

In the area of cognitive functioning, children who later develop schizophrenia tend to perform below their healthy siblings and classmates. These cognitive deficits are reflected in lower scores on measures of achievement, poorer grades in school, and a lower childhood IQ compared with peers who do not go on to develop schizophrenia (Aylward, Walker, & Bettes, 1984; Dickinson, 2014; Jones, Rodgers, Murray, & Marmot, 1994). However, results are mixed and a recent meta-analysis shows no significant difference in performance on general academic achievement tests or mathematic achievement tests between those who go on to develop schizophrenia and those who do not (Dickinson et al., 2012). Specifically, research suggests early impairment in verbal knowledge, visual knowledge, simple reasoning skills, and a worsening trajectory of speeded performance, working memory, and complex problem solving (Dickinson, 2014; Richenber et al., 2010). Children who later are diagnosed with schizophrenia also show abnormalities in social behavior. They are less responsive in social situations, show less positive emotion (Walker & Lewine, 1990; Walker, Grimes, Davis, & Smith, 1993), and have poorer social adjustment than children with healthy adult outcomes (Done, Crow, Johnstone, & Sacker, 1994). In our studies of the childhood home movies of patients with schizophrenia, we found that the children who develop schizophrenia later in life showed more negative facial expression of emotion than did their siblings as early as the first year of life, indicating that the vulnerability for schizophrenia is subtly manifested in the earliest interpersonal interactions (Walker et al., 1993).

Vulnerability to schizophrenia is also apparent in motor functions. When compared with their siblings with healthy adult outcomes, children who develop schizophrenia show more delays and abnormalities in motor development, including deficits in the acquisition of early motor milestones, such as bimanual manipulation and walking (Walker, Savoie, & Davis, 1994). Deficits in motor function extend throughout the premorbid period (Walker, Lewis, Loewy, & Palyo, 1999), and persist after the onset of the clinical illness (McNeil, Cantor-Graae, & Weinberger, 2000). Furthermore, abnormal gesture behavior has been observed in both premorbid (Mittal, Tessner et al., 2006; Mittal, Walker et al., 2010) and unmedicated individuals with schizophrenia (Troisi, Spalletta, & Pasini, 1998). These data imply that the movement abnormalities recognized in schizophrenia are likely to have complex interactions with language and motor planning centers.

It is important to note that neuromotor abnormalities are not pathognomonic for schizophrenia, in that they are observed in children at risk for a variety of disorders, including learning disabilities, and conduct and mood disorders. But they are one of several important clues pointing to the involvement of brain dysfunction in schizophrenia. Further, although medication-induced movement abnormalities, such as tardive dyskinesia, involve characteristic motor signs, these are not to be confused with involuntary movements which have been demonstrated to be present in drug-free groups such as at-risk infants (Fish, 1987), at-risk adolescents (Walker, Lewis et al., 1999), and never medically treated schizophrenia patients (Khot & Wyatt, 1991).

Despite the subtle signs of abnormality that have been identified in children at risk for schizophrenia, most of these children do not manifest diagnosable mental disorders in childhood. Thus, while their parents may recall some irregularities in their development, most children who eventually develop schizophrenia were not viewed as clinically disturbed in childhood. But the picture often changes in adolescence. Many adolescents who go on to develop schizophrenia show a pattern of escalating adjustment problems (Walker & Baum, 1998). They show a gradual increase in feelings of depression, social withdrawal, irritability, and noncompliance. This developmental pattern is not unique to schizophrenia: adolescence is also the critical period for the expression of the first signs of mood disorders, substance abuse, and other mental disorders. As a result, researchers view adolescence as a critical period for the emergence of various kinds of behavioral dysfunction (Corcoran et al., 2003; Walker, 2002).

Among the behavioral risk indicators sometimes observed in "pre-schizophrenic" adolescents are "subclinical" signs of psychotic symptoms. These signs comprise the risk state that is now referred to as "ultra-high risk" or APS in the DSM-5 research section (American Psychiatric Association, 2013; described in the section on "Classification," above) and is considered to represent the putative prodromal stage of psychosis. Specifically, these symptoms are termed attenuated positive symptoms, and in research clinics typically fall under one of the following five subgroups: unusual thought content, suspiciousness/paranoia, grandiosity, perceptual abnormalities, or disorganized communication (Gee and Cannon, 2012). For APS criteria, the individual must experience the presence of symptoms at least once per week in the last month and the onset of the symptoms must be in the last 12 months or symptoms must have worsened in the last 12 months (Tsuang et al., 2013). These individuals tend to exhibit declining social and role functioning along with the subthreshold psychotic symptoms. Furthermore, research suggests that the neurocognitive and social-cognitive performance of youth with APS is somewhat between that of healthy controls and patients with schizophrenia. Although this risk period requires further study, the most recent meta-analysis suggests that approximately 18% of those identified as APS will convert to a psychotic disorder within the first 6 months and 36% after 3 years (Fusar-Poli et al., 2012). Research indicates that with each year, there is a reduction in this risk of conversion to a psychotic disorder, but it remains unclear whether seeking help/treatment is responsible for this decrease in psychosis transition or whether a certain portion of these individuals identified as at-risk would never have converted (i.e. false positives; Yung et al., 2007).

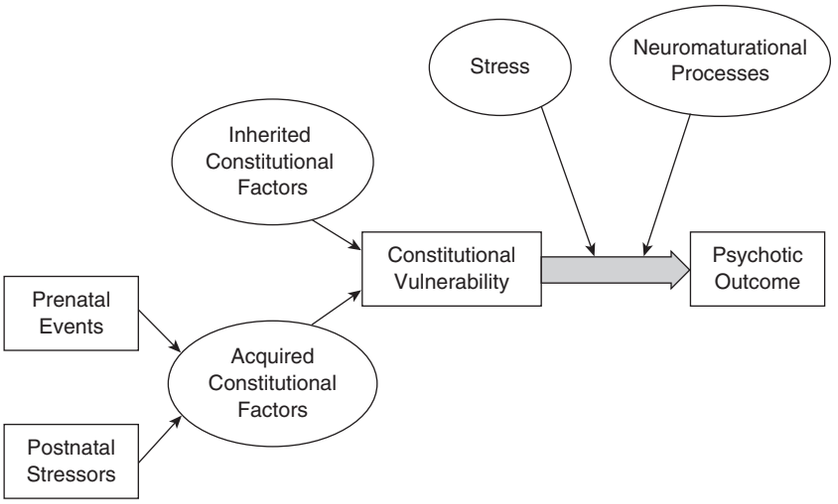

Figure 17.1 A diathesis-stress model of the etiology of schizophrenia.

Illness Onset The picture that has emerged to describe illness onset is best described in the framework of the diathesis-stress model that has dominated the field for several decades (Walker & Diforio, 1997; Walker, Mittal & Tessner, 2008).

Figure 17.1 illustrates a contemporary version of the diathesis-stress model. This particular model postulates that constitutional vulnerability (i.e., the diathesis) emanates from both inherited and acquired constitutional factors. The inherited factors are genetically determined characteristics of the brain that influence its structure and function. Acquired vulnerabilities arise mainly from prenatal events that compromise fetal neurodevelopment.

Whether the constitutional vulnerability is a consequence of genetic factors or environmental factors, or a combination of both, the model assumes that vulnerability is, in most cases, congenital. But the assumption that vulnerability is present at birth does not imply that it will be clinically expressed at any point in the life span. Rather, the model posits that two sets of factors determine the postnatal course of the vulnerable individual. First, external stressors influence the expression of the vulnerability. Although this is a long-standing assumption among theorists, it is important to clarify it. Empirical research has provided evidence that episodes of schizophrenia follow periods of increased life stress (Horan et al., 2005; Ventura, Nuechterlein, Hardesty, & Gitlin, 1992). Nonetheless, there is no evidence that individuals affected by schizophrenia experience more stressful events, perhaps with the exception of childhood trauma, than individuals without schizophrenia, but rather that they are more sensitive to stress when it occurs (Holtzman et al., 2013). This assumption is the essence of the model; the interaction between vulnerability and stress is critical.

Diathesis-stress models have incorporated mechanisms to account for the adverse impact of stress on brain function (Walker & Diforio, 1997; Walker, Mittal, & Tessner, 2008). The HPA axis, which is responsible for the release of cortisol and other stress hormones, has been examined as one of the primary neural systems triggered by stress exposure, leading to the expression of vulnerability for schizophrenia (Walder, Walker, & Lewine, 2000). Results from this research indicate that psychotic disorders are associated with elevated baseline and challenge-induced HPA activity, that antipsychotic medications reduce HPA activation, and that agents that augment stress hormone release exacerbate psychotic symptoms (Walker, Mittal et al., 2008).

In addition, the model assumes that neuromaturation is a key element. In particular, adolescence/early adulthood appears to be a critical period for the expression of the vulnerability for schizophrenia. Thus, some aspects(s) of brain maturational processes during the post-pubertal period are likely playing an important role in triggering the clinical expression of latent liabilities (Corcoran et al., 2003; Insel, 2010; Walker, Kestler, Bollini, & Hochman, 2004).

The onset of the first episode of schizophrenia may be sudden or gradual. There is some evidence that longer untreated psychotic episodes may be harmful for patients with schizophrenia and may result in a worse course of illness (Davidson & McGlashan, 1997; Harris et al., 2005; Perkins et al., 2004). However, this conclusion is controversial, and some researchers suggest that the relation between longer duration of untreated psychosis and worse prognosis may be a product of poorer premorbid functioning and an insidious onset (Larsen et al. 2001). Nonetheless, early intervention is important, regardless of the specific causal factors, as recent evidence suggests that duration of untreated psychosis is indeed a significant predictor of outcome and that the relationship between duration and functioning may be mediated by the presence of negative symptoms (Hill et al., 2012).

People with schizophrenia vary in their course of illness and prognosis. Being male, having a gradual onset, an early age of onset, poor premorbid functioning, and

a family history of schizophrenia are all associated with poorer prognosis (Gottesman, 1991). In addition, some environmental factors contribute to a worse outcome. For example, patients with schizophrenia who live in homes where family members express more negative emotion are more likely than those with supportive families to have more frequent relapses (Rosenfarb, Bellack, & Aziz, 2006; Butzlaff & Hooley, 1998).

Exposure to stress can exacerbate schizophrenia symptoms. Researchers have found an increase in the number of stressful events in the months immediately preceding a schizophrenia relapse (Horan et al., 2005; Ventura et al., 1992). Finally, there is a rapidly accumulating body of research indicating that heavy, consistent cannabis use is associated with a threefold increase in risk of schizophrenia, earlier onset of disorder in vulnerable individuals, and exacerbation of psychotic symptoms (Manrique-Garcia et al., 2012; Rey, Martin, & Krabman, 2004;). There is some evidence showing that patients with schizophrenia who started using cannabis early and chronically in life had better neurocognitive performance than patients who used later on, showing that this early cannabis use group may have a specific, less-impaired neurocognitive profile (Yücel et al., 2012).

As outlined, the prognosis for many schizophrenia patients is poor. Around 20% of individuals with schizophrenia may become homeless within the first year of diagnosis (Folsom et al., 2005). Within the first 5 years, 13.7% are able to achieve full remission of symptoms along with adequate social/role functioning, and within 25 years around 30% are able to achieve a favorable long-term outcome (Harrison et al., 2001; Robinson et al., 2004). Further, patients with schizophrenia often suffer from comorbid (i.e., co-occurring) conditions. For example, the rate of substance abuse among patients with schizophrenia is very high, with as many as 50% of all patients with schizophrenia and 90% in prison settings meeting lifetime DSM-IV criteria for substance abuse or dependence (Regier et al., 1990; Thoma and Daum, 2013).

Suicide is the leading cause of death among people with schizophrenia. It has been estimated that 50% of patients with schizophrenia attempt suicide and 4–5% successfully commit suicide (Donker et al., 2013). Risk factors associated with suicide in this population include previous attempts, more severe depressive symptoms, being male, having an earlier onset, suffering recent traumatic events, and recent hospitalization (Schwartz & Cohen, 2001; Donker et al., 2013). Further, the risk of suicide for individuals with schizophrenia is increased in the earlier stages of illness, and particularly within the first year of diagnosis (Donker et al., 2013).

Evidence-Based Interventions

Researchers have not yet identified any biological or psychological cures for schizophrenia. However, significant progress has been made in treatments that greatly improve the prognosis of the illness. As a result of this research progress, the quality of life for individuals with schizophrenia is dramatically better than it was at the turn of the 20th century.

The first issue to be addressed in the evaluation and treatment of schizophrenia is safety. The risk of self-harm and potential for violence must be assessed (McGirr et al., 2006; Siris, 2001). A medical examination is typically conducted to rule out other illnesses that can cause or exacerbate psychotic symptoms. This examination includes a review of the medical history, a physical examination, and laboratory tests. Many patients with schizophrenia have untreated or undertreated medical conditions such as nutritional deficiencies and infections that are a result of their psychological and/or socio-economic limitations (Goff, Heckers, & Freudenreich, 2001).

If a patient is not at acute risk to self or others, the next consideration becomes the type of treatment that would be most beneficial. There are several factors to consider. These include the person's living situation (many patients with schizophrenia are homeless), level of insight, willingness to accept treatment, past treatment history, financial resources, including health insurance, and family and other available social support. To increase chances of success, the patient with schizophrenia should be encouraged to talk openly about their treatment preferences, beliefs about medication, and concerns about side effects or changes.

The treatment of schizophrenia can be divided into three phases: the acute, stabilization, and maintenance phases (Sadock & Sadock, 2000). In the acute phase, the goal of treatment is to reduce the severity of symptoms. This phase is usually 4–8 weeks in duration. In the stabilization phase, the goal is to consolidate treatment gains. This usually takes about 6 months. Finally, during the maintenance phase, the symptoms are in remission (partial or complete). At this point, the goal of treatment is to prevent relapse and improve functioning.

Biological/Pharmacological Interventions The mainstay of the biological treatment of schizophrenia is antipsychotic medication. First developed in the 1950s, these medications had an enormous impact on the lives of people afflicted with schizophrenia. Their psychotic symptoms improved and many were able to leave psychiatric hospitals (deinstitutionalization). The first effective biological treatment for schizophrenia, chlorpromazine (Thorazine®), was the first in a line of medications now referred to as the "typical" antipsychotics or "neuroleptics." All of these medications act by blocking activity in the dopamine system. The typical antipsychotic medications are classified as high, medium, and low potency, and differ from each other in adverse-effect profiles (Table 17.2). High-potency neuroleptics tend to carry a higher risk of extrapyramidal effects (e.g., motor abnormalities), and are prescribed in low dosages. Some examples of high-potency agents are fluphenazine (Prolixin®),

trifluoperazine (Stelazine®), and haloperidol (Haldol®). Low-potency neuroleptics are prescribed in higher milligram doses and have lower risk of motor effects, but a higher risk of inducing seizures, antihistaminic effects (including sedation and weight gain), anticholinergic effects (including cognitive dulling, dry mouth, blurry vision, urinary hesitancy, and constipation), and antiadrenergic effects (including postural hypotension and sexual dysfunction). Examples of low-potency neuroleptics include chlorpromazine, and thioridazine (Mellaril®). Medium-potency agents tend to have adverse effects intermediate between the low- and high-potency drugs. Examples of these include: perphenazine (Trilafon®), and loxapine (Loxitane®).

In the 1990s, a new generation of antipsychotic medications became available for therapeutic use in Europe and North America. The new class of medication is commonly referred to as "atypical" or "second-generation" antipsychotics. Medications in this class share a lower risk of both the early occurring and the late emerging (or tardive) movement disorders, although recent evidence suggests there is some variation within the atypical antipsychotics as to their ability to cause these extrapyramidal effects (Rummel-Kulge et al., 2012). The atypical antipsychotics include risperidone (Risperdal®), olanzapine (Zyprexa®), olanzapine/fluoxetine (Symbyax®), quetiapine (Seroquel®), ziprasidone (Geodon®), aripiprazole (Abilify®), paliperidone (Invega®), asenapine (Saphris®), iloperidone (Fanapt®), lurasidone (Latuda®), and clozapine (Clozaril®). The individual medications differ significantly from one another in the neurotransmitter receptors that they occupy. Although all block dopamine neurotransmission to some extent, they vary in the extent to which they affect serotonin, glutamate and other neurotransmitters. These atypical antipsychotics have become the first line of treatment for schizophrenia. The efficacy of the atypical antipsychotics for the treatment of positive symptoms is at least equivalent to that of the typical antipsychotics. Some studies suggest that they are more effective for negative symptoms and the cognitive impairments associated with the disorder, although findings are mixed and inconclusive (Forster, Buckley, & Phelps, 1999; Kane & Correll, 2010; Sadock & Sadock, 2000). Of practical clinical significance, however, is the substantial risk of developing a "metabolic syndrome" related to the use of this class of medicines. Recent research has revealed that the atypical antipsychotics carry an elevated risk of substantial weight gain, new onset or worsening diabetes mellitus, and lipid abnormalities (Newcomer, 2005).

Antipsychotic medications are usually administered orally. For patients who are not compliant with oral medication, injectable, long-lasting (depot) antipsychotic medication may be administered (usually every 2–4 weeks). Six depot neuroleptics are commercially available in the United States. Two are first-generation or "typical" antipsychotics and four are second-generation or "atypical" antipsychotics. Benefits of depot neuroleptics include the ease of use for the patient, and the fact that compliance is easily monitored by the clinician. The risks are similar to the risks of all of the "typical" antipsychotics. The only additional risk is that of localized pain or swelling at the injection site.

Drug-induced movement disorders can be divided into acute and late onset syndromes. Acute, or early emerging motor symptoms include pseudo-Parkinsonism, bradykinesias (decreased movement), rigidity, and dystonic reactions (sudden onset of sustained intense, uncontrollable muscle contraction commonly occurring in the facial and neck muscles). Tardive dyskinesia is a late emerging syndrome that includes irregular choreiform (twisting, or worm-like) movements that usually involve the facial muscles, but can involve any voluntary muscle group. It is fortunate that the rate of tardive dyskinesia has declined since the introduction of atypical neuroleptics. It is important to note the these drug-induced movement abnormalities are a distinct and separate entity from the spontaneous movement abnormalities noted earlier, which occur as a natural correlate of schizophrenia.

Mention should also be made of the neuroleptic malignant syndrome. This is a rare, idiopathic, life-threatening

TABLE 17. 2
Selected Antipsychotic Drugs (from Sadock and Sadock, 2000 p. 1204)

Drug	Route of administration	Usual daily oral dose	Sedation	Autonomic	Extrapyramidal adverse effects
Chlorpromazine	Oral, IM	200–600	+++	+++	++
Fluphenazine	Oral, IM, depot	2–20	+	+	+++
Trifluoperazine	Oral, IM	5–30	++	+	+++
Perphenazine	Oral, IM	8–64	++	+	+++
Haloperidol	Oral, IM, depot	5–20	+	+	+++
Loxapine	Oral, IM	20–100	++	+	++
Olanzapine	Oral	7.5–25	+	++	0?
Quetiapine	Oral	150–750	++	++	0?
Risperidone	Oral	2–16	+	++	+
Clozapine	Oral	150–900	+++	+++	0?

IM = intramuscular

complication of neuroleptic medication. It is characterized by mental status changes (delirium), immobility, rigidity, tremulousness, staring, fever, sweating, and autonomic instability (labile blood pressure and tachycardia). Laboratory investigations often reveal an elevated white blood cell count (in the absence of infection), and an elevated creatine phosphokinase level. Treatment involves discontinuation of neuroleptic medication, supportive medical treatment, a peripheral muscle relaxant, and bromocriptine (a D2 receptor agonist; Rosebush & Mazurek, 2001).

Psychosocial Treatments of Schizophrenia Although antipsychotic medication is the crucial first step in the treatment of schizophrenia, there is substantial evidence that psychosocial interventions can also be beneficial for both the patient and the family. It is unfortunate that such treatments are not always available because of limited mental health resources. Nonetheless, it is generally agreed that the optimal treatment approach is one that integrates pharmacologic and psychosocial interventions.

Research supports the use of family therapy, which includes psychoeducational and behavioral components, in treatment programs for schizophrenia (Bustillo, Lauriello, Horan, & Keith, 2001). Family therapy has been shown to reduce the risk of relapse, reduce family burden, and improve family members' knowledge of and coping with schizophrenia. Briefly, treatment includes psychoeducation about symptoms, diagnosis, and prognosis, along with therapeutic modules focusing on communication and problem solving skills.

Comprehensive programs for supporting the patient's transition back into the community have been effective in enhancing recovery and reducing relapse. One such program, called assertive community treatment, was originally developed in the 1970s by researchers in Madison, Wisconsin (Udechuku et al., 2005; Bustillo et al., 2001; Saddock & Sadock, 2000). Acceptance and commitment therapy (ACT) is a comprehensive treatment approach for the seriously mentally ill living in the community. Patients are assigned to a multidisciplinary team (nurse, case manager, general physician, and psychiatrist) that has a fixed caseload and a high staff/patient ratio (1:12). The team delivers all services to the patient when and where he or she needs it, and is available to the patient at all times. Services include home delivery of medication, monitoring of physical and mental health status, *in vivo* social skills training and frequent contact with family members. Studies suggest that assertive community treatment can reduce time spent in hospital, improve housing stability, and increase patient and family satisfaction. Research shows that such treatment can aid in the stable living in a community, but has little impact in other areas such as social functioning and employment (Mueser, Deavers, Penn, & Cassisi, 2013).

Social skills training seeks to improve the overall functioning of patients by teaching the skills necessary to improve performance of activities of daily living, employment related skills, and interaction with others. Research indicates that social skills training can improve social competence in the laboratory and in the clinic, along with impacting social/daily living skills, community functioning and negative symptoms (Bustillo et al., 2001; Kurtz & Mueser, 2008; Penn & Mueser, 1996). There is also some evidence to suggest that combining social skills training with attention training can enhance outcomes (Silverstein et al., 2008).

The rate of competitive employment for the severely mentally ill has been estimated at less than 20% (Lehman, 1995; Marwaha & Johnson, 2004); thus, vocational rehabilitation has been a major focus of many treatment programs. Some evidence suggests that "supported employment programs" produce better results than traditional vocational rehabilitation programs as measured by patients' ability to obtain competitive, independent employment and increased wages earned (Bond, Drake & Becker, 2012; Mueser et al., 2013).

Cognitive-behavior therapy for schizophrenia draws on the tenets of cognitive therapy that were originally developed by Beck and Ellis (Beck, 1976; Ellis, 1986). The theory is that normal psychological processes can help maintain or reduce specific psychotic symptoms. Cognitive-behavioral therapy (CBT) for psychosis challenges the notion of a discontinuity between psychotic and normal thinking. The normal cognitive mechanisms that are already being used in the non-psychotic aspects of the patient's thinking can be used to help the psychotic individuals deal directly with their symptoms (Kingdon & Turkington, 2005). The choice of target symptoms is based on the patient's preference and/or severity of the problems created by the psychotic symptom in question. Psychotic beliefs are never directly confronted, although specific psychotic symptoms such as hallucinations, delusions, and related problems are targeted for intervention by means of education and cognitive restructuring skills around the symptoms, their onset, along with providing insight into how the behavioral framework of antecedents, beliefs, and consequences functions in psychosis (ABC model; Dickerson, 2000). There have been somewhere near 40 randomized controlled trials evaluating the efficacy of CBT for psychosis. A recent review (Mueser et al., 2013) noted that CBT was linked to decreases in psychotic symptoms, negative symptoms, and mood problems, as well as better social functioning. However, findings comparing CBT with other active treatments are mixed and currently somewhat inconclusive, as most studies of the efficacy of CBT where compared to treatment as usual (Mueser et al., 2013). Further, one meta-analysis suggests that CBT only has a small therapeutic effect for psychosis, which is made even smaller when acknowledging biases in research methodology (Jauhar et al., 2014).

Within this cognitive-behavioral framework, another therapeutic modality, ACT, has shown some promise in treating psychosis. ACT works within the context of CBT and emphasizes increased awareness and openness, psychological flexibility, living in-line with one's values,

and finding actions that are workable. The original studies found that receiving ACT was associated with lower rates of hospitalization and decreases in psychotic symptoms (Bach & Hayes, 2002; Gaudiano & Herbert, 2006). More recent findings indicate long-term decreases in hospitalization following a trial of ACT, although findings using this approach are still new, limited, and warrant future attention (Bach, Hayes, & Gallop, 2011).

Biological/Pharmacological and Psychosocial Treatment for Prodromal Populations Several reports indicate that antipsychotics may be effective in reducing the progression of prodromal syndromes into psychotic disorders. A review of several recently completed randomized clinical trials with antipsychotic medication reports that following the end of treatment, antipsychotic medication as a pre-psychotic intervention may delay the onset of psychosis or ameliorate pre-psychotic symptoms (de Koning et al., 2009). However, most studies find no significant differences at the end of follow up 1–4 years later. Although the onset may be delayed, there is no indication that psychosis is prevented.

It is also important to acknowledge the potential risks of antipsychotic medications when used as a preventative intervention (Corcoran et al., 2010). The adverse effects of second-generation antipsychotics include extrapyramidal symptoms, weight gain, and metabolic complications. With no proven long-term effects, the benefit/risk ratio of using antipsychotics as a pre-psychotic intervention must be weighed carefully. We also do not yet know the effects of these medications on prodromal adolescents. As our knowledge of the effects of psychotropic medication on adolescent growth and development increases, we will be in a better position to weigh any adverse effects against potential benefits, both short term and long term (Jensen et al., 1999).

There are considerably fewer randomized controlled trials evaluating psychosocial treatments for the prodromal population compared with patients with schizophrenia. The limited research base has primarily evaluated CBT, supportive therapy, integrative therapy, and cognitive remediation. The findings from these treatment studies suggest that while short-term benefits may be found, lasting effects past 12 months were not apparent in most studies. The exception was from one study evaluating integrated therapy (combining CBT, skills training, cognitive remediation, and family education), where benefits lasted up to 24 months, and another study where trending effects were noted at 18 months for CBT (Addington et al., 2011; Bechdolf et al., 2012; Morrison et al., 2007; van der Gaag et al., 2012). There is also a recent emphasis on highlighting the family as a means of intervention in the prodromal phase. Research is currently underway to examine whether family focused treatment (Miklowitz, George, Richards, Simoneau, & Suddath, 2003) may help to delay or prevent the onset of psychosis (Schlosser et al., 2012).

Cognitive Remediation and Other Promising New Interventions Additionally, cognitive remediation therapy has also received attention with over 40 randomized controlled trials published evaluating its use in treating psychosis. Cognitive remediation generally takes the form of computerized tasks aimed at enhancing specific cognitive skills such as attention, working memory, or planning. The origins of cognitive remediation for schizophrenia come from research showing the brain to be plastic (i.e., able to be changed by behavior and experience). Results find that cognitive remediation significantly improves cognition, with mixed findings on whether functioning is affected (Mueser et al., 2013; Wykes et al., 2005). There is some evidence to suggest that cognitive remediation may allow for the acquisition of new skills and improved functioning by combining it with other empirically supported treatments (Mueser et al. 2013). There has been a focus on usage of omega-3 fatty acids to prevent transition to psychosis, following a randomized controlled trial showing significantly less conversion to psychosis in individuals who received omega-3 treatment (Amminger et al., 2010). Finally, exercise is also being investigated as an intervention in prodromal populations and individuals diagnosed with schizophrenia, owing to research linking aerobic activity with the reversal of brain abnormalities commonly seen in schizophrenia (i.e., increases in hippocampal gray matter following exercise; Mittal, Gupta et al., 2013; Pajonk et al., 2010).

Summary

This chapter has reviewed a broad range of scientific research on the nature and origins of schizophrenia. Spanning over a century, the efforts of investigators have yielded, piece by piece, a clearer view of the illness. The puzzle is not solved, but we can certainly claim progress toward a solution.

In summary, although we have not found all the pieces of the puzzle, we have made significant progress in moving toward a comprehensive account of the etiology of schizophrenia. Among the mental disorders, schizophrenia remains a clear illustration of the complex interactions taking place between the individual and the environment. In the coming years, we can expect research to yield important information about the precise nature of the brain vulnerabilities associated with schizophrenia, and the mechanisms involved in the interaction of congenital vulnerability with subsequent life stress and neuromaturation. Genetic data and research into gene expression will provide insight into etiology, as well as further our understanding of the role neurotransmitter abnormalities in schizophrenia. Longitudinal studies conducted during the prodromal period hold strong promise of elucidating the complicated interactions between development (e.g., hormones, neural maturation), and latent constitutional vulnerabilities. Furthermore, research during this period holds strong potential to inform the next

generation of psychosocial and pharmacological preventive interventions.

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