Schizophrenia is the most crippling of the psychiatric disorders. It typically strikes as adulthood is approaching and is likely to be disabling for a lifetime. Schizophrenia occurs in all countries, cultures, and socioeconomic classes. It affects both sexes equally, although typical age of onset appears to be younger in males (about 21 years) than in females (closer to 27 years) (Hochman & Lewine, 2004). Contrary to many historical explanations, it is now widely believed that a disease of the brain most often causes schizophrenia.

The prevalence of schizophrenia worldwide is commonly accepted to be about 1% of the population (Arajarvi et al., 2005; Kulhara & Chakrabarti, 2001). Because schizophrenia eliminates or severely limits the most productive years of an individual’s life and may require lifelong family or institutional care, its costs to society are enormous. The excess annual cost of an average schizophrenia patient (about $15,500) is considerably higher than annual costs of other major mental disorders such as depression ($4,500; Wu et al., 2005). When considering direct health care costs (e.g., drugs, outpatient care, hospital inpatient stays, long-term care), direct non-health-care costs (e.g., law enforcement, research and training, homeless shelters), and indirect costs (e.g., unemployment, reduced productivity at work, premature mortality, caregiver), the national cost associated with schizophrenia becomes astounding; researchers considering these different sources have made estimates as high as $180.8 billion in the United States alone (Wu et al., 2005). Unfortunately, the current government funding does not reflect these enormous costs; the National Institute of Mental Health is able to allocate only roughly $74 per patient to schizophrenia research.

The imbalance between costs and funding reflects the fact that schizophrenia has been misunderstood and stigmatized from the time it was first identified until the present. In many cultures, as early as ancient Egypt and as recently as Europe in the Middle Ages, individuals with schizophrenia were regarded as being possessed by evil spirits or the devil. In some primitive cultures this has led to such individuals being treated with a privileged status (e.g., as tribal spiritual guides/shamans), but far more often schizophrenic individuals were treated quite brutally. For example, for about 200 years in Europe, dating from the mid-1400s to the mid-1600s, the mentally ill were persecuted, were burned as witches, and, when hospitalized, were “restrained, often by chains; whipped; ill fed; unwashed; and treated with bloodletting, purgatives, and other ‘curative’ tortures. Those who were not hospitalized wandered the countryside unattended, scorned, beaten” (Gottesman, 1991, p. 11). Although the past century has seen a substantial increase in public awareness and general understanding of mental illness, many individuals with schizophrenia still face significant challenges. Today, as a reflection of governmental...
mental health care policy, a substantial proportion of the homeless, populating the streets of urban areas, living under bridges, in cardboard boxes, or in subway tunnels, are also suffering from schizophrenia. Also disturbing is the trend that suggests that because of mid-1980s-era deinstitutionalization (whereby a large proportion of the federally and state-funded live-in mental health care facilities were shut down in favor of a community mental health care/outpatient model), prisons have become the de facto health care provider. Although there has always been debate regarding this legislative decision, trends noted in the past decade have really shed light on the long-term ramifications of closing down residential treatment facilities; at the present time 1.25 million inmates in prisons around the United States suffer from debilitating disorders such as schizophrenia (Stephney, 2007).

Even though many treatment advances have been made in the last half century, schizophrenia remains a chronic debilitating illness with a guarded outcome. Further progress in treating and, perhaps, in preventing this illness will require a more complete understanding of its causes and pathophysiology. Currently, progress in understanding the biology of schizophrenia has been rapidly evolving, and emerging new findings in genetics, brain functioning (including neurocognition and neuroimaging), neuroendocrinology, and prevention give considerable reason to be optimistic. In this chapter, we provide a historical background and then explore promising research directions.

History of the Clinical Disorder

Emil Kraepelin (1856–1926), a German psychiatrist, is credited with initiating the modern approach to schizophrenia. Kraepelin (1971) spent his career formulating detailed descriptions of the clinical characteristics and course of various forms of mental illness. He called the disorder dementia praecox, or early dementia, to reflect what he considered the typical course of the disease; that is, an early onset followed by a progressively deteriorating course leading to dementia. He also recognized that dementia praecox was different from mental illnesses characterized by an intermittent course and essentially emotionally based symptoms (e.g., euphoria and depression). He labeled the latter illness manic-depression. According to Andreasen (1984, p. 16), “Kraepelin’s recognition of these two illnesses within the confusing array of patients living in the nineteenth and early twentieth-century psychiatric hospitals laid the foundations of modern psychiatry.”

It is particularly interesting that Kraepelin viewed the most likely cause of schizophrenia to be some type of physiological abnormality. He was also the first to establish subtypes of schizophrenia based on differences in symptom patterns. According to his nosology, the illness was divided into catatonic, hebephrenic, and paranoid forms.

Another major historical figure is Eugen Bleuler (1857–1939), a Swiss psychiatrist. Bleuler added a fourth diagnostic category, simple schizophrenia, to Kraepelin’s nosology and renamed the illness schizophrenia in recognition that patients did not all display the deterioriative course defined by Kraepelin. In translation, this has sometimes led to a misunderstanding of the illness. The word schizophrenia is derived from two Greek roots: 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. In the lay press, and especially in movies, a major misconception is that this implies a “split personality” (or, in more contemporary terms, multiple personality disorder, or dissociative identity disorder). Multiple personality disorder, however, is unrelated to schizophrenia. Rather, Bleuler was referring to a fundamental splitting of various aspects of the mind, such as between thoughts and emotions.

Bleuler adopted a more “psychological” view of schizophrenia than had Kraepelin. Whereas Kraepelin had based diagnosis on symptom course (i.e., poor outcome), Bleuler’s primary criterion was the presence of a disordered thought process, which he considered to consist of a loosening of associations (e.g., connecting unrelated ideas); autism (self-centeredness); affective disturbance (inappropriate or constricted emotions); and ambivalence (Gottesman, 1991). He believed that the symptoms described by Kraepelin, such as hallucinations and delusions, were secondary, resulting from the thought disorder. Bleuler also believed that schizophrenia consisted of a heterogeneous cluster of illnesses, that is, the “group of schizophrenias” (Bleuler, 1950),
with different etiologies, symptom patterns, and course. The formulations of both Kraepelin and Bleuler provided the foundations for much of the subsequent research on schizophrenia.

Contemporary Clinical Views

Clinically, schizophrenia is a complex illness. There is no laboratory test to confirm the diagnosis, and schizophrenia is characterized by a diversity of symptoms, no one of which is definitive, and many of which are also found in other neurological or psychiatric disorders. The course of the disorder is also variable; it can start either abruptly or insidiously, with outcome ranging from full or partial recovery to total debilitation. Consistent with Bleuler, most researchers continue to regard schizophrenia as a heterogeneous disorder, with different etiologies, pathophysiology, and outcome. As a result, diagnostic precision is difficult. This, in turn, greatly complicates the study of the disorder.

Following Kraepelin and Bleuler, there have been additional attempts to subtype schizophrenia on the basis of symptom patterns in order to reduce the illness to categories more easily studied and understood. For example, in the 1960s, several classifications were based on the longitudinal course of illness and variably divided it into acute versus chronic, process versus reactive, or good versus poor prognosis (Andreasen & Olsen, 1982). These categories, however, were not markedly successful in reflecting etiology and have given way to the more current division of the disorder into positive and negative syndromes (described below).

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 had a major impact on the criteria for schizophrenia contained in contemporary diagnostic systems, including DSM-IV.

Using DSM-IV criteria, schizophrenia can be diagnosed when signs and symptoms of the disorder have been present for 6 months or more (including prodromal and residual phases). The characteristic symptom criteria for schizophrenia include the following: (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).

Hallucinations and delusions are the most dramatic features and the hallmark characteristics of schizophrenia. Hallucinations involve hearing, seeing, feeling, or smelling things that are not, in reality, present. Of these, the most common type of hallucination consists of hearing voices, one or several, typically making commentaries about the individual or conversing with each other. Delusions are fixed, unshakable beliefs that are not grounded in reality. The most common types of delusions are persecutory (e.g., believing that one is being investigated by the government or involved in an elaborate conspiracy), grandiose (e.g., belief that one has special powers), or somatic (e.g., belief that one’s body has been changed in some way). To provide an illustration of symptoms and symptom clusters described in detail below, we have selected a number of vignettes taken from a series in Schizophrenia Bulletin entitled “First Person Account,” wherein patients describe their own conceptualizations of what has happened to them. In the following section, the patient describes delusions of a persecutory nature, which also hold a component of somatic concern; this is highly illustrative of the complicated patterns of symptoms that patients often present:

All of a sudden things weren’t going so well. I began to lose control of my life and, most of all, myself. I couldn’t concentrate on my schoolwork, I couldn’t sleep, and when I did sleep, I had dreams about dying. I was afraid to go to class, imagined that people were talking about me and on top of that I heard voices. I called my mother in Pittsburgh and asked for her advice. She told me to move off campus into an apartment with my sister. After I moved in with my sister, things got worse. I was afraid to go outside and when I looked out of the window, it seemed that everyone outside was yelling “kill her, kill her.” My sister forced me to go to school. I would go out of the house until I knew she had gone to work then I would return home. Things continued to get worse. I imagined that I had a foul body odor and I sometimes took up to six showers a day. I recall going to the grocery store one day and I imagined that the people in the store were saying “get saved, Jesus is the answer.” . . . I tried to tell my sister about it, but she didn’t understand. She suggested that I see a psychiatrist, but I was afraid
The following vignette describes this paranoid experience, including delusions and hallucinations.

I had one particular friend. I called him the “Controller.” He was my secret friend. He took on all of my bad feelings. He was the sum total of my negative feelings and my paranoia. I could see him and hear him, but no one else could. The problems were compounded when I went off to college. Suddenly, the Controller started demanding all my time and energy. He would punish me if I did something he didn’t like. He spent a lot of time yelling at me and making me feel wicked. I didn’t know how to stop him from screaming at me and running my existence. It got to the point where I couldn’t decipher reality from what the Controller was screaming. So I withdrew from society and reality. I couldn’t tell anyone what was happening because I was so afraid of being labeled as “crazy.” I didn’t understand what was going on in my head. I really thought that other “normal” people had Controllers too. (Jordan, 1995, p. 502)

In the following vignette, Brodoff (1988) describes visiting his brother, who is suffering from schizophrenia, at a locked facility.

Some months after Andy was first institutionalized, I went to visit him in the hospital. With a shaved head, a jagged front tooth (a relic of his days rootlessly roaming around Times Square) and gestures that had the diffuse, futile energy characteristic of old men, my brother seemed like a homeless vagabond. His eyes were both vacant and haunted with the naked look of a frightened animal frozen by the beam of approaching headlights. He was pathetically docile, parroting back my words and gestures as though he didn’t know where my identity left off and his own began (p.114).

It is important to emphasize that, despite advances in diagnosis, clinicians still do not know the diagnostic boundaries of schizophrenia. Moreover, the boundaries between schizophrenia and mood disorders are 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-IV-TR 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. Interestingly, the prognosis for patients with schizoaffective disorder is, on average, somewhere between that of schizophrenia and the mood disorders.

Etiology of Schizophrenia

It is now widely accepted that schizophrenia is a disease of the brain. However, after close to 100 years of study, the cause of this disease remains a mystery. Throughout this time, it has been well known that schizophrenia runs in families, but whether this is due to shared environment or shared genes was subject to question. For many years, the psychoanalytic tradition guided the search for environmental causes. As a result, a great deal of attention was directed at identifying bad parenting or other family interactions as the source of illness. A leading contender was the influence of the “schizophrenogenic mother,” variously described as emotionally cold, distant, rejecting, or as communicating mixed messages (e.g., Fromm-Reichmann, 1948). These notions have now been discarded. No evidence has ever been found to indicate that rearing factors can, in and of themselves, directly cause schizophrenia. Similarly, there has been no support that other, quite plausible, negative environmental experiences, such as extreme poverty or severe childhood trauma, can alone induce schizophrenia.

Researchers now know, based on over four decades of behavioral genetic research using family, twin, and adoption methods, that schizophrenia involves a major genetic component (Gottesman, 1991). Thus, etiology is most productively viewed as a complex interplay between a number of factors, including genetics, family environment, and early development, that confer a constitutional vulnerability to later illness (Mednick et al., 1998). For example, it has been established that 10% to 15% of children of a parent with schizophrenia also develop the illness. The question, however, is whether this increased rate (only 1% of the general population develops schizophrenia) is due to problems associated with growing up with an ill parent or is largely determined by genetics.
Genetic Factors

During the years that environmental explanations were studied and discarded, a great deal of evidence gradually accumulated indicating that schizophrenia runs in families because it involves a genetic component. This does not imply genetic determinism but, rather, that an abnormality in one or more genes leads to a biological predisposition or susceptibility for developing the illness. This predisposition may not be sufficient in itself to cause schizophrenia but probably requires some kind of “trigger,” such as exposure to prenatal insults. This view is known as the diathesis-stress theory of illness and has been an influential etiological model for at least 20 years.

Family, Twin, and Adoption Studies

The classic genetic methodologies—family, twin, and adoption studies—provided the initial evidence for the heritability of schizophrenia.

Family Studies

Figure 12.1 (adapted from Gottesman, 1991, p. 96) summarizes the risks for developing schizophrenia in various relatives of an index patient with schizophrenia. This summary pools information from about 40 studies conducted in European populations between 1920 and 1987. Reprinted with permission from Gottesman, I. I. (1991). Schizophrenia genesis: The origins of madness. New York: Freeman.

![Figure 12.1](image-url)
Western Europe from 1920 through 1987. Gottesman explains his exclusive reliance on European studies on the basis that in the countries involved (a) diagnoses tend to be conservative and based on similar criteria; (b) compared to the United States, the populations are more stable, homogeneous, and often more cooperative; and (c) researchers have access to national health registers not available in the United States.

Relatives are shown in order of increasing risk for schizophrenia. As can be seen, this is impressively consistent, with risk for illness increasing as the degree of genetic relatedness to the index subject becomes closer. At the top of the figure is the general population risk of 1%. The risks for second-degree relatives (who share 25% of their genes) range from 2% to 6% and are therefore only slightly higher than the general population risk. First-degree relatives (who share approximately 50% of their genes), by contrast, show a considerably higher risk rate, ranging from 9% for siblings to close to 50% for the offspring of two schizophrenic parents. In the case of monozygotic (MZ) twins (who share 100% of their genes), risk for schizophrenia is also at the elevated rate of about 50%. However, the fact that the MZ twin risk rate is far below 100% suggests that environmental factors also play an important role in the expression of illness. Gottesman concludes that

Overall, the pattern of risk figures in the relatives of schizophrenics strongly supports the conclusion that the magnitude of the increased risk varies with the amount of gene sharing and not with the amount of experience sharing. Identical twins and offspring of dual matings have higher risks than do first-degree relatives, who have higher risks than do second-degree relatives, who have higher risks than do third-degree relatives, who have higher risks than do spouses and the basic risk of 1 percent in the general population. (Gottesman, 1991, pp. 97–98)

The relevant studies reported since Gottesman concluded his review do not change these conclusions appreciably. Early genetic studies (e.g., Kendler, 1988) also led to the notion of a spectrum of schizophrenia-related disorders, consisting of a cluster of illnesses that are clinically similar to schizophrenia and are found to characterize the relatives of schizophrenic patients. These disorders, consisting primarily of paranoid, schizoid, and schizotypal personality disorders (SPD), are typically less severe and share a common genetic etiology with the core schizophrenia illness. There is consensus that schizotypal personality disorder falls into this spectrum (Battaglia, Bernardeschi, Franchini, Bellodi, & Smeraldi, 1995; Siever et al., 1990). More controversy surrounds the inclusion of other conditions such as schizoid personality disorder (Levinson & Mowry, 1991; Mittal, Kalus, Bernstein, & Siever, 2007).

Twin Studies Because twins with schizophrenia are relatively rare and twin studies of schizophrenia are therefore very difficult to conduct, only a limited number of such studies have been conducted since the early 1900s. A twin study conducted in Denmark by Gottesman and Bertelsen (1989) is particularly supportive of the importance of genetic factors. In this study, the offspring of MZ and DZ twins discordant for schizophrenia, originally evaluated by Fischer (1971), were clinically followed up 18 years later. Gottesman and Bertelsen reported the rather extraordinary finding that, whereas for the ill MZ twins the rate of schizophrenia among their offspring was 16.8%, the rate of illness among offspring of the well MZ co-twins was 17.4%. Thus the disease genotype (identical in MZ twins) had the same rate of transmission to the offspring regardless of whether it was clinically expressed in the parent. However, the same pattern was not found for the discordant DZ twins. In this case, the rate of illness in the offspring of the ill twin was 17.4%, but only 2.1% of the children of the healthy DZ co-twins became ill, the same as the rate reported more generally for nieces and nephews of schizophrenics (see Figure 12.1).

To fully understand these findings, it is important to make a distinction between the genotype and the phenotype. The genotype is the underlying genetic constitution of the individual. The phenotype refers to the observable characteristics or behaviors of an individual. The extent to which the genotype is expressed behaviorally (i.e., by the phenotype) depends on a number of additional biological and environmental factors. In the twin study just described, it appears that for the “healthy” MZ co-twins, the disease genotype was present but clinically silent. However, the genotype was transmitted to the next generation to the same extent as it was for the affected MZ parents, resulting in the same rate of illness among offspring, whether the twin parent was phenotypically sick or healthy. Gottesman thus concludes that
The data we have shown from this unusually well-followed-up sample of Danish schizophrenic twins and their offspring support a strong role for genetic factors in the etiology of schizophrenia. No support is found for the suggestion that rearing by a schizophrenic parent is necessary or sufficient to produce schizophrenia in offspring. (Gottesman, 1991, p. 124)

In summary, the results from the twin studies that have been conducted over the past century provide strong evidence that schizophrenia is indeed heritable. However, because MZ twins are far from being 100% concordant for illness (concordance rates are roughly 48% for MZ twins and 17% for DZ twins), genetics can be only part of the explanation. It is clear that other factors are also involved (Gottesman, 1991).

Adoption Studies A third source of support for the genetics of schizophrenia comes from adoption studies. The first adoption study was conducted in Oregon by Heston (1966), who assessed the rate of illness in the adult offspring of schizophrenic mothers. All of the children had been adopted or placed in orphanages before they were 4 days old. Heston found that 10.4% of the 47 adopted-away offspring of schizophrenic mothers were themselves schizophrenic compared to none of the 50 adopted-away offspring of matched normal mothers. Investigators from the United States and Denmark replicated Heston’s results (e.g., Lowing, Mirsky, & Pereira, 1983; Rosenthal et al., 1968).

Kety and colleagues (Kety, 1988) pioneered an alternate adoption research strategy. Also conducted in Denmark, this study focused on adults with a diagnosis of schizophrenia who had been adopted as young children. The question asked was what the rates of schizophrenia were in the biological versus the rearing parents of these individuals. Kety found that the rate of schizophrenia-related illness (5.4%; e.g., schizotypal personality disorder, schizoaffective disorder) among the adoptive relatives (i.e., the relatives who had raised the schizophrenic index patients) was the same as the rate in the control populations. By contrast, a much higher rate (21.4%) was found for the biological relatives of the patients. In their diagnostically updated reanalysis, Kendler and Gruenberg (1984) again found a significantly higher rate of schizophrenia-related disorders among the biological relatives of the schizophrenic adoptees than among the relatives who had adopted them.

In an important study, Tienari and colleagues (1994) followed a sample of Finnish adults who had been born to mothers with schizophrenia and then adopted at early ages. It was found that even though there was little to no schizophrenia in the adoptive rearing families, the at-risk children later developed significantly higher levels of psychosis than found in similarly adopted offspring of normal parents. However, closer examination revealed that a determining factor for the development of psychosis was the quality of the home environment, such that the high-risk children raised in disturbed adoptive families were more likely to develop schizophrenia (Tienari et al., 1994). Note that the direction of causality has not been definitively established, because symptom development in the adopted offspring might have been the primary cause of family disruption. Similarly, a Danish study following the offspring of parents with schizophrenia showed that participants were more likely to develop schizophrenic symptoms if they were raised in institutional rather than in familial environments (Walker, Cudeck, Mednick, & Schulsinger, 1981). Studies such as these have demonstrated the interplay between genetic susceptibility and environmental influences and reveal a considerably more complex picture of schizophrenia.

In summary, the preceding family, twin, and adoption studies have made a solid case for the genetic etiology of schizophrenia within the diathesis-stress model. These early findings paved the way for the more recent linkage studies described next.

Mode of Transmission Although it is now commonly accepted that schizophrenia involves a genetic component, no simple Mendelian mode of transmission fits the data (McGuffin & Sturt, 1986). The unresolved issue of heterogeneity further complicates the picture. It remains to be determined whether schizophrenia is a single disease entity or a cluster of illnesses with different etiologies, some genetic and others environmental (sometimes referred to as phenocopies).

The two types of transmission most frequently hypothesized have been the single gene model and the multifactorial/polygenic model. It has appeared unlikely from the earliest family data that a single gene (or single major locus, SML) model can explain the transmission of risk for schizophrenia. Nevertheless, some researchers maintained the possibility of a SML by introducing the concept of incomplete penetrance. This is the notion that although the gene is present, it may not be fully
expressed clinically (i.e., that not everyone who has the gene will get the illness).

Gottesman introduced the alternative polygenic/multifactorial threshold model into the field of schizophrenia (Gottesman & Shields, 1967). According to this model, a complex illness such as schizophrenia is the result of the interaction of several small genes as well as other factors.

These polygenes are not different in kind from the major genes that cause Mendelian conditions, but each has only a small effect on trait variation as compared to the total variation for that trait. Therefore, the expression of the trait depends much less on which polygenes in the specific system a person has . . . than on the total number pulling him or her toward an extreme. A feature of special interest in the study of schizophrenia and other major mental disorders is the ability of such polygenic systems to store and conceal genetic contributors to the liability to developing the disorder, somewhat analogous to carrier status for recessive diseases. (Gottesman, 1991, p. 88)

As further explained by McGuffin and Sturt (1986, p. 70):

In general, it is assumed that there is a single continuous variable, termed liability to develop the disorder, which is contributed by the predominantly additive effects of many genes at different loci. . . . As a result, liability within the population at large tends to follow a normal distribution. Only those individuals whose liability falls beyond a certain threshold manifest the disorder.

In other words, what the individual inherits is a liability or predisposition for developing the disease, not the disease itself. The liability increases the risk that the individual will develop schizophrenia, but whether or not the illness will actually be expressed depends on many other factors, both biological and environmental. This model is consistent with the patterns of familial transmission observed for other complex physical diseases such as diabetes, coronary heart disease, epilepsy, and some forms of mental retardation.

More Recent Genetic Developments The introduction of molecular genetic techniques has made it possible to look for the location in the genome of schizophrenia illness genes, that is, where such genes are localized on specific chromosomes. As described by Malhotra and Goldman (1999), the basic strategy in linkage analysis is to identify alleles (alternate forms of a gene at a given locus) that are shared by ill relatives more often than would be predicted by chance. Individual families with ill members are specifically studied, with the optimal families being those that contain multiple ill relatives through generations or affected relative pairs. Linkage refers to the identification of a chromosomal region that is associated or “linked” with the behavior (or phenotype) of interest. This area on the chromosome may contain hundreds of genes. While successfully used for a number of illnesses, such as Huntington’s disease (Gusella et al., 1983) and cystic fibrosis (Tsui et al., 1985), linkage findings for schizophrenia have thus far been inconsistent. Possible problems restricting effectiveness of the linkage approach include the necessity to specify a genetic model (e.g., dominant vs. recessive, not yet known), low power to detect genes of small effect, and because identifying and recruiting families with many ill members is very difficult (Malhotra & Goldman, 1999).

As a result, more recent techniques, known as association studies, attempt to identify specific or “candidate” genes. Association studies have the advantages of studying ill individuals compared to healthy controls and thus do not require the involvement of extended families. Unlike linkage analysis, which is essentially a random search for markers of the phenotype, association studies are hypothesis driven. A candidate gene can be selected for study based on previous linkage findings indicating it is located near to an established marker on a chromosome or can be selected on the basis of a biological function associated with the gene’s product (i.e., protein). At present, using association techniques, a number of plausible candidate genes have been identified, including neuregulain, DISC-1, COMPT, and so on (for a review see Ishizuka, Paek, Kamiy, & Sawa, 2006). Although none of these findings are yet conclusive, the strides being made are rapid and compelling, and they offer considerable promise that a more complete understanding of the biology of schizophrenia is just around the corner.

Prenatal Factors Contribute to Constitutional Vulnerability

There is evidence to suggest that a key component in the etiology of psychosis is what occurs during the prenatal and/or perinatal period. Exposure to a teratogen during gestation can severely interfere
with central nervous system development. Studies described here draw direct links between second-trimester prenatal insult (a period of significant CNS development) and later emerging putative markers associated with schizophrenia (e.g., HPA dysregulation, movement abnormalities; for a review see Mittal, Dhruv, Tessner, Walder, & Walker, 2007). Along these lines, animal models have demonstrated that time-sensitive and regionally specific types of prenatal insult have significant repercussions for the later development of key neural structures, such as the hippocampus (for a review, see Maestripieri & Wallen, 2003). Large-scale epidemiological studies have indicated that nonoptimal prenatal environments (e.g., poor maternal nutrition) are highly predictive of later developmental problems. Furthermore, complications during delivery are predictive of later developmental difficulties. Within the context of the model presented in this chapter, one strong possibility is that a genetic predisposition in the child might result in prenatal susceptibility to these events. To provide a framework for understanding a neural diathesis-stress model of psychosis etiology, the following section provides an integration of research findings in this area.

Prenatal and Perinatal Insult

There is extensive evidence that obstetrical complications (OCs) have an adverse impact on the developing fetal brain and may contribute to vulnerability for schizophrenia. Birth cohort studies have shown that schizophrenia patients are more likely to have a history of OCs (Buka, Tsuang, & Lipsitt, 1993; McNeil, 1988; Dalman, Allebeck, Cullberg, Grunewald, & Koster, 1999; Takagai et al., 2006). Included among these are prenatal conditions, such as toxemia and preeclampsia, and labor and delivery complications. A review of the OC literature by Cannon (1997) concluded that, among the different types of OCs, those that are often associated with fetal hypoxia (oxygen deprivation) were the most strongly linked with later schizophrenia. In general, the odds of developing adult onset schizophrenia appear to increase linearly with an increasing number of hypoxia-related OCs (Cannon, Hollister, Bearden, & Hadley, 1997; Zornberg, Buka, & Tsuang, 2000).

Studies of rodents and nonhuman primates have shown that prenatal maternal stress can interfere with fetal brain development, and that it is associated with elevated glucocorticoid release and hippocampal abnormalities in the offspring (Coe et al., 2003; Smythe, McCormick, Rochford, & Meaney, 1994; Weinstock, 1996). 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 found higher rates of schizophrenia in the offspring of women whose spouses died during their pregnancies (Huttunen, 1989) and in women who were exposed to a military invasion during their pregnancies (van Os & Selten, 1998). It is likely that prenatal stress triggers the release of maternal stress hormones, which can disturb fetal neurodevelopment and subsequent functioning of the hypothalamic-pituitary-adrenal axis and in turn influence behavior and cognition (Welberg & Seckl, 2001).

Another prenatal event that has been linked with increased risk for schizophrenia is maternal viral infection. Researchers have found that the risk rate for schizophrenia is elevated for individuals born shortly after a flu epidemic (Barr, Mednick, & Munk-Jorgensen, 1990; Brown et al., 2004; Limosin, Rouillon, Payen, Cohen, & Strub, 2003; Murray, O’Callaghan, Castle, & Lewis, 1992;) or after being prenatally exposed to rubella (Brown, Cohen, Harkavy-Friedman, & Babulas, 2001). The critical period of exposure appears to be between the 4th and 6th months of pregnancy.

Mednick and his colleagues (Mednick, Machon, Huttunen, & Bonett, 1988) determined the rates of schizophrenia in offspring who were in utero during the Helsinki influenza epidemic of 1957 and compared the rates to those of controls. The sample was divided according to trimester of exposure. The rates of schizophrenia for offspring of mothers exposed to the influenza virus during the first or third trimesters were not different from those of controls. However, the rates for the offspring exposed during the second trimester were substantially higher. The results suggest that the second trimester is a critical period of vulnerability. Studies from other geographic regions have also shown increased risk of schizophrenia with exposure to influenza during the second trimester (Barr et al., 1990; Brown et al., 2004; O’Callaghan, Sham, Takei, Glover, & Murray, 1991), but there have been some failures to replicate as well (Crow, 1994). Most of the evidence across studies suggests that a virus may lead to disruption of neural development in the second trimester and that this disruption is linked to the eventual development of schizophrenia.
Influenza epidemics are rare and these viruses probably account for a small proportion of the total number of patients with schizophrenia worldwide. Even with a substantial increase in risk over baseline, only a small minority of mothers who were exposed to the virus in the second trimester gave birth to a preschizophrenic child. Nonetheless, the results from the influenza studies are important because they show that a particular environmental factor occurring at a specific time in fetal development can increase risk for schizophrenia.

The findings from research on prenatal viral infection might help explain the “season-of-birth” effect in schizophrenia. Several studies have found that a disproportionate number of schizophrenic patients are born during the winter months (Bradbury & Miller, 1985; Narita et al., 2000; Torrey, Miller, Rawlings, & Yolken, 1997). 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. Disruptions during this stage may give rise to brain abnormalities that confer vulnerability.

Additional support for the relationship between second trimester fetal insult and schizophrenia comes from the observation that individuals with schizophrenia show subtle physical aberrations or asymmetries in features of the head and limbs, often referred to as minor physical anomalies (MPAs). Given that both external craniofacial and limb features and the CNS originate in the same germinal (ectoderm) layer, and in the same period of gestational development, the presence of MPAs is assumed to be an outward manifestation of abnormal CNS development and, consequently, a physical manifestation of abnormal fetal brain development (Ismail, Cantor-Graae, & McNeil, 2000; Mittal, Dhruv, et al., 2007; Smith, 1982). Supporting this notion, among individuals with schizophrenia, MPAs are associated with an earlier age of onset, presumably reflecting heightened constitutional vulnerability (Green, Satz, Soper, & Kharabi, 1987). Further support comes from a recent prospective longitudinal investigation following 265 individuals in a high-risk Danish sample (children of patients with schizophrenia), which noted that individuals with a high number of MPAs developed schizophrenia and spectrum disorders significantly more often than they developed other physical or mental illnesses and significantly more often than a no mental illness outcome (Schiffman et al., 2002).

One of the chief questions confronting researchers is whether OCs act independently to increase risk for schizophrenia or have their effect by interacting with a genetic vulnerability. One possibility is that the genetic vulnerability for schizophrenia involves an increased sensitivity to prenatal factors that interfere with fetal neurodevelopment (Cannon, 1997, 1998; Preti, 2005; Walshe et al., 2005). Genes associated with the immune response are potential candidates; individuals with certain genotypes may be more sensitive to the adverse effects of prenatal exposure to maternal viral infection. For example, researchers have recently posited that functional polymorphisms on interleukin genes are candidates (Brown, 2006).

It is also plausible that obstetrical events act independently of genetic vulnerabilities, although such effects would likely entail interactions among multiple obstetrical factors. For example, in order to produce the neurodevelopmental abnormalities that confer risk for schizophrenia, it may be necessary for a specific OC to occur during a critical period of cellular migration and/or in conjunction with other factors such as maternal fever or immune response.

Prenatal nutritional deficiency has also been linked with an elevated rate of schizophrenia in offspring. Toward the end of World War II, a military blockade led to the Dutch Hunger Winter, a severe famine in this region from October 1944 until May 1945. Just as in the influenza studies in Helsinki, it is possible to follow the offspring of women who were pregnant during the Hunger Winter to examine the risk for development of subsequent psychiatric disorders (Susser & Lin, 1992). The offspring of women who were exposed to severe famine had increased rates of hospitalization for schizophrenia compared to controls. Unlike the influenza studies, the increased risk occurred for offspring who were exposed during the first trimester. If starvation exerts its risk at a slightly earlier period of development (i.e., first vs. second trimester), it could indicate that the period of risk varies according to the type of neurodevelopmental stressor.

More recently, McClellan and colleagues (McClellan, Susser, & King, 2006) hypothesized that in utero exposure to maternal starvation may lead to de novo mutations in genes critical for brain development. Further, starvation-induced folate deficiency could mediate this risk by impairing the capacity for DNA repair, thus altering gene expression (McClellan et al., 2006). This focus on gene expression...
mechanisms is a promising area for future research on schizophrenia.

As in the case of prenatal viral exposure, prenatal starvation interrupting normal brain development probably accounts for only a small proportion of individuals who develop schizophrenia. Furthermore, the majority of individuals exposed to such insults do not develop schizophrenia. Therefore, prenatal events cannot be the only explanation, and many researchers believe that these events precipitate illness only in individuals who already have some type of biological predisposition for schizophrenia.

Cognition in Schizophrenia

For the outsider looking on, the patient is talking and simply stops, the idea he was trying to communicate simply terminated. But this is not so. The idea has not been obliterated, but conquered by forces in the brain that have the power to halt meaningful communication and block the schizophrenic's connection with the very person or persons he wishes so desperately to hold on to. He is tortured as his voice turns mute and he sees his lifelines being cut by his own inability to complete the fervent thoughts that now choke him. I am often caught in guttural struggles with my own voice as I try to get the words out. These aborted thoughts, not lost, but taken over by a more powerful chaos, are among the things that cannot be said. (Ruocchio, 1991, p. 357)

This vignette is illustrative of the impact that cognitive deficits can have on individuals with schizophrenia. In recent years, the amount and scope of research on cognition in schizophrenia has substantially increased. As described previously, schizophrenia is well known for its dramatic clinical features, including positive, negative, and disorganized symptoms. Although researchers have not traditionally viewed schizophrenia as a neurocognitive disorder, they now recognize that cognitive performance impairments in schizophrenia are a part of the illness (Green, 2001). Cognitive studies in schizophrenia can provide valuable information with respect to the nature, genetics, disability, and prognosis of the illness. For example, understanding cognitive impairment in schizophrenia can help to reveal core aspects of the illness, endophenotypes for use in genetic studies (a hereditary characteristic associated with a specific condition, but is not a direct symptom of that condition—representative of simpler clues to the genetic underpinnings than the disease syndrome itself), and help to determine obstacles to community reentry. Origins of the literature on cognition in schizophrenia can be traced back 100 years to early theorizing about the disorder.

Bleuler (1950) helped to shape current views of neurocognition in schizophrenia by making a key distinction between accessory and fundamental symptoms of schizophrenia. Accessory symptoms included hallucinations, delusions, and a variety of behavioral and speech abnormalities. Fundamental symptoms were divided into simple and compound symptoms. Simple fundamental symptoms included disturbances in association, affectivity, and ambivalence; and these simple fundamental symptoms combined to form compound fundamental symptoms that included disturbances in attention. Bleuler used the term attention broadly to refer to lack of responsiveness to the environment as well as a diminution in attentional resources.

Bleuler introduced several concepts that form the basis for modern views of cognition in schizophrenia. First, he suggested that certain basic dysfunctions (simple symptoms) could be assembled into compound symptoms, including disordered attention. Second, Bleuler considered psychotic symptoms such as hallucinations and delusions to be secondary to fundamental symptoms. This hierarchy of symptoms was both insightful and counterintuitive: He proposed that the most dramatic features of the illness (i.e., hallucinations and delusions) were one step removed from the disease process. Bleuler suggested that schizophrenia could be best understood by a focus on core features of the illness, rather than on the more noticeable defining features of the disorder. The content of the secondary symptoms are largely based on chance, not predetermined: “Almost the totality of the heretofore described symptomatology of dementia praecox is a secondary, in a certain sense, an accidental one” (1950, p. 349). Third, he emphasized different time courses of fundamental versus accessory symptoms. Enduring features of the illness were considered more central to the disorder than episodic features: “The primary symptoms are the necessary partial phenomena of a disease; the secondary symptoms may be absent, at least potentially, or they may change without the disease process having to change at the same time” (Bleuler, 1950, p. 349).
Characteristics of Cognitive Impairment in Schizophrenia

Because the cognitive impairments in schizophrenia were so clearly described a century ago by Bleuler and Kraepelin, the recent surge of interest in this area is more of a rediscovery than a discovery. One reason for the increasing interest is that cognitive impairments are now clearly viewed as “core” features of the illness and not as secondary features of the illness. When people talk about a core feature in this context, it means that the impairments are not merely a result of psychotic symptoms (e.g., distractibility due to hallucinations) or a result of psychopharmacological treatments (e.g., sedation due to antipsychotic medications). Evidence that cognitive impairment is a core feature of schizophrenia comes from several lines of research that are briefly listed here and more completely described elsewhere (Braff, 1993; Gold, 2004; Gold & Green, 2004; Green, 2007; Nuechterlein, Dawson, & Green, 1994).

1. Many patients demonstrate cognitive or intellectual impairments before the onset of psychotic symptoms and other clinical features of the disorder; hence the cognitive impairments predate, and show a different time course than, clinical features of illness.

2. Cognitive impairment (at attenuated levels) can be detected in first-degree relatives of schizophrenic patients who are not psychiatrically ill. This suggests that some of the impairments reflect predisposition to schizophrenia, as opposed to the presence of the illness. For this reason, cognitive impairment is being used as an endophenotype in genetic studies of schizophrenia.

3. The magnitude of the cognitive impairment is relatively stable across clinical state, with the level of impairment on some cognitive measures being quite similar when patients move in and out of psychotic episode. Hence, the impairments can occur in the absence of clinical symptoms of schizophrenia.

4. Cross-sectional correlations between cognitive performance and ratings of psychotic symptom severity are typically very small. The low correlations are especially true for positive symptoms. Correlations with negative and disorganized symptoms are sometimes larger but still relatively modest.

5. The effects of antipsychotic medications are much larger on positive symptoms of schizophrenia than they are on cognition. The literature is inconsistent in showing greater cognitive benefits for second-generation medications (i.e., atypicals) compared to first-generation medications. Even if the newer drugs have cognitive benefits, this discrepancy of cognitive and clinical effects is true for both types of drugs. It suggests that the antipsychotic medications act on different neural systems than those that underlie the cognitive impairments.

The cognitive deficits associated with schizophrenia are fairly broad and encompass a wide range of domains. It is estimated that 90% of patients have clinically meaningful deficits in at least one cognitive domain and that 75% have deficits in at least two (Palmer et al., 1997). It is possible that even these relatively high rates of impairment are underestimates and that even patients who perform in the normal range might do more poorly than they would were they not affected. This interpretation is based on rather consistent findings that patients tend to perform poorly when compared with siblings, including unaffected MZ twins (Goldberg et al., 1990), or when compared to estimates of expected levels based on premorbid functioning (Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000).

Two Approaches to Cognition in Schizophrenia

Modern studies of cognition in schizophrenia have emerged from two distinct traditions: clinical neuropsychology and experimental cognitive psychology. We describe each of them briefly.

Clinical Neuropsychology  During much of the twentieth century, brain damage was generally viewed as a single phenomenon (i.e., organicity). Organic conditions were thought to reflect a central defect that was common across patients with different types of brain damage (K. Goldstein, 1939). When clinical neuropsychology assessments were applied to schizophrenia patients, it was mainly to assist in differential diagnosis, particularly in distinguishing between “organic (neurological)” versus “functional (psychiatric)” conditions (G. Goldstein, 1978). Tests were developed to distinguish brain-damaged patients from psychiatric patients and healthy adults.
This particular goal for neurocognitive assessment was mainly unsuccessful, and it largely disappeared as the field’s knowledge of neurological and psychiatric conditions increased. An understanding of psychiatric disorder, including schizophrenia, from a brain-based perspective replaced assumptions that were rooted in nonbiological and psychoanalytic traditions.

Neurocognitive assessment has increasingly provided quantitative and clinically meaningful information on various types of brain functions. In the 1970s and 1980s, standardized batteries, such as the Luria-Nebraska Neuropsychological Battery (Golden, Purisch, & Hammek, 1985) or the Halstead-Reitan Battery (Reitan & Wolfson, 1978), were a preferred approach. These batteries assess a wide range of cognitive functions using standardized sets of tests. Because of limitations in using a highly structured and predetermined approach (Lezak, 1995), preference has grown for a process approach that includes flexible batteries that vary according to the clinical questions posed by a particular patient.

Neurocognitive assessment is now rarely used for differential diagnosis with schizophrenia. Instead, it is used primarily to quantify the severity of impairment in clinically relevant domains of cognitive functioning. The advantages of tests developed in the clinical neuropsychology approach is that they usually have desirable psychometric properties (e.g., good test-retest reliability) and norms that can be used to generate standardized scores from raw scores. The cognitive domains of interest for psychopathology are, for the most part, the same domains that are of interest for other conditions, including neurological disorders or learning disabilities. Based on a careful literature review and consensus meetings sponsored by the National Institute of Mental Health (NIMH), several cognitive domains were selected as important to assess in treatment studies of cognition in schizophrenia: speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Nuechterlein et al., 2004).

Although there are considerable differences from patient to patient, there is a typical neurocognitive profile in schizophrenia that is characterized by larger deficits (in the range of 1.5 SDs or more) in verbal learning and vigilance, and lesser impairments in visual organization abilities and vocabulary (Heinrichs & Zakzanis, 1998).

Experimental Cognitive Psychology  A second approach has grown from experimental cognitive psychology, which emphasizes the assessment and understanding of normal human cognition and the refined assessment of key cognitive constructs. The experimental psychology approach to schizophrenia has evolved steadily over the past 50 years as experimental psychopathologists have attempted to provide parsimonious accounts for the huge range of cognitive deficits in schizophrenia with overarch- ing explanations, such as deficits in “segmental set,” “filtering” (McGhie & Chapman, 1961), “abstraction” (K. Goldstein, 1939), or the presence of “overinclusive” thinking (Payne, Mattussek, & George, 1959). The experimental approach seeks to document, characterize, and determine the nature of cognitive deficits in the disorder. In general, measures developed in this approach emphasize precision in measuring a construct more than psychometric properties or norms. More recently, the experimental psychology approach has capitalized on methods from cognitive neuroscience, including neuroimaging and electrophysiology.

Studies in experimental psychopathology tend to be viewed within the models of experimental psychology that are prominent at the time. As models of human cognition have evolved in the experimental literature, so too have the models used to understand deficits in schizophrenia. In the 1970s and 1980s, two models of normal cognition influenced many studies: capacity models and stage models. The capacity models emphasize the overall processing capacity of the individual (Kahneman, 1973). From this perspective, deficits in schizophrenia can be attributed to a decrease in the overall amount of processing resources or to an inefficient allocation of finite resources (Nuechterlein & Dawson, 1984). Stage models involve a series of processing stages; information is transformed at each stage and then fed to subsequent stages. As applied to schizophrenia, the goal of stage models is usually to identify the earliest stage of dysfunction. The notion is that a dysfunction at an early stage will cause poor information to be passed along, disrupting later processing stages.

Subsequent models combine features of both and offer considerable value for understanding abnormalities or attentional function. Cowan’s (Cowan, 1988) integrative model of attentional functioning, for instance, has several major components including a brief sensory store, memory components, and a central executive. Related developments have occurred in other areas. For example, a model of context processing has been used to explain attentional
and working memory deficits in schizophrenia (Carter, Kerns, & Cohen, 2004). Also, sophisticated dual-task paradigms have been used to specify bottlenecks in processing (Nuechterlein et al., 1994; Nuechterlein, Pashler, & Subotnik, 2006).

By using cognitive models, the experimental psychology approach helps us to map a large variety of deficits on a smaller number of model components and to understand the connections among different components. Without such models, the diversity of neurocognitive deficits in schizophrenia appears haphazard.

**Cognition and Functional Outcome**

Functional outcome in schizophrenia, including social connections, vocational status, and degree of independent living, has been disappointing and a source of public health concern (Hegarty, Baldessarini, Tohen, Waternaux, & Oepen, 1994; Helgason, 1990; Wiersma et al., 2000). The antipsychotic medications that were introduced in the 1950s largely controlled psychotic symptoms for a majority of patients, but individuals with schizophrenia still generally have considerable difficulty achieving adequate community functioning. In fact, schizophrenia is one of the largest causes of disability among all illnesses for young adults (Murray & Lopez, 1996). Psychotic symptoms are not strong determinants of community functioning; if they were, controlling symptoms would lead to improved functional outcomes. Other factors are determinants of community functioning, including cognitive impairment.

Cognitive deficits have highly consistent relationships to a range of functional outcomes, including community functioning and skill acquisition in psychosocial rehabilitation (Green, 1996; Green, Kern, Braff, & Mintz, 2000; Green, Kern, & Heaton, 2004). Whereas the associations tend to be medium in strength for individual cognitive domains, they can be large when multiple cognitive domains are combined into composite scores (Green et al., 2000). These relationships appear not only in cross-sectional assessments but also prospectively (Green, Kern, et al., 2004). Some studies have found good associations with outcome 2 to 4 years after baseline assessment, an interval that is long enough to see changes in functional status (Dickerson, Boronow, Ringel, & Parente, 1999; Friedman et al., 2002; Gold, Goldberg, McNary, Dixon, & Lehman, 2002; Robinson, Woerner, McMeniman, Mendelowitz, & Bilder, 2004; Stirling et al., 2003).

Associations between cognitive performance and functioning are not specific to schizophrenia, as they also occur for various neurological disorders (including multiple sclerosis, HIV infection; Rao, Leo, Ellington, & Nauertz, 1991; Van Gorp, Baerwald, Ferrando, McElhiney, & Rabkin, 1999), as well as in normal aging (Moritz, Kasl, & Berkman, 1995). Researchers know much less about other psychiatric disorders, but the initial findings suggest similar cognition–function relationships for bipolar disorder (Dickerson et al., 2004; Martínez-Arán et al., 2004).

**Treatments for Cognitive Impairment in Schizophrenia**

Because cognitive impairment is considered to be a core feature of schizophrenia and because it is related to community functioning, it has become a target for intervention. The hope is that improving cognition in schizophrenia will open the door to improved social and vocational functioning. For example, “atypical” antipsychotics, introduced into clinical use within the past decade, have proved to be an effective antipsychotic with less motoric side effects, a greater 5-HT antagonistic effect, and a somewhat lower DA antagonist effect than typical antipsychotics (Remington, 1995). Although these improvements significantly help with symptoms, current antipsychotic medications have relatively little impact on the cognitive deficits, so the development of new drugs to enhance cognition in schizophrenia has become both a scientific focus and a public health priority.

Until recently, notable obstacles prevented any drug from receiving approval from the U.S. Food and Drug Administration (FDA) for the purpose of improving cognition in schizophrenia (Hyman & Fenton, 2003). In the absence of a pathway for FDA approval, the pharmaceutical industry was understandably reluctant to make the necessary investment in cognition-enhancing drugs for schizophrenia. To stimulate the development of new drugs in this area, the NIMH launched the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Initiative (Carpenter, 2004; Marder & Fenton, 2004). Through a series of meetings with representatives of industry, academia, and government, MATRICS was charged with reaching consensus on the methods and measures to be used to evaluate promising new cognition-enhancing drugs for schizophrenia. The goal was to build a pathway for drug approval by the FDA.
One essential product of the NIMH MATRICS Initiative was a consensus cognitive battery to be the standard performance outcome measure for clinical trials of cognition enhancing drugs for schizophrenia: the MATRICS Consensus Cognitive Battery (MCCB) (Green, Nuechterlein, et al., 2004; Nuechterlein & Green, 2006). As noted above, several cognitive domains were selected including speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Nuechterlein et al., 2004). In addition, recommendations were made regarding optimal clinical trial designs (Buchanan et al., 2005) in this area and for prioritizing neuropharmacological targets (special issue of *Psychopharmacology*, 174[1], June 2004). MATRICS consensus meetings generated increased interest in this area, and several studies are currently underway to develop novel drugs for cognition in schizophrenia.

Aside from current efforts to develop new drugs for cognition in schizophrenia, nonpharmacological approaches are also being developed and tested. The results of cognitive remediation in schizophrenia have been variable, but are generally positive (Kurtz, Moberg, Gur, & Gur, 2001; Medalia, Revheim, & Casey, 2001; Twamley,Jeste, & Bellack, 2003; Wexler & Bell, 2005). Several studies have combined cognitive remediation with psychosocial or vocational interventions, again with some promising results (Bell, Bryson, Greig, Corcoran, & Wexler, 2001; McGurk, Mueser, Feldman, Wolfe, & Pascaris, 2007; Wexler & Bell, 2005). In addition to training in basic neurocognition (e.g., training on attention and memory), efforts are underway to develop methods to improve social cognition. Such interventions include training to identify emotion expressed in faces or to correctly attribute mental state in others (Horan, Kern, Penn, & Green, in press; Penn, Roberts, Combs, & Sterne, 2007; Wolver et al., 2005).

The pharmacological and nonpharmacological approaches to intervention for cognition are unlikely to remain separated much longer. There is a growing realization that cognition-enhancing drugs will do little good in isolation. To see meaningful effects of drug treatments, it is likely patients will need to be actively engaged in learning or training. Although the beneficial effects of cognition-enhancing drugs will be seen on cognitive performance measures, translation of these benefits to community functioning will likely require active training and learning opportunities (e.g., psychosocial rehabilitation, cognitive remediation). Hence, the recent concentration on developing new drugs for cognition in schizophrenia will also increase focus on nonpharmacological approaches to intervention.

**Abnormalities Revealed by Structural Neuroimaging**

Structural neuroimaging of schizophrenia has employed two techniques: computerized tomographic (CT) scans and magnetic resonance imaging (MRI). CT scanning was the predominant imaging procedure from its first applications in the mid-1970s (Johnstone, Crow, Frith, Stevens, & Kreel, 1976) until the late 1980s, when MRI largely replaced it. MRI has superior spatial resolution compared to CT; because MRI does not involve any radiation, it is more suited to repeat scans. In general, the findings from these two techniques are comparable. In the following sections, major findings from the structural neuroimaging literature of schizophrenia will be summarized by the type of abnormality and then by the brain region of interest.

**Types of Abnormalities in Schizophrenia**

Several reliable findings can be extracted from the large number of neuroanatomical studies in schizophrenia. First, schizophrenic patients generally have larger ventricles than do healthy control subjects, with a group difference of roughly 0.70 SD (McDonald et al., 2006; Raz & Raz, 1990). The ventricles are four structures inside the brain filled with cerebrospinal fluid that apparently function to cushion and nourish. In studies of schizophrenia, the ventricles serve as important indexes of brain atrophy, because they are often enlarged when surrounding regions of the brain are smaller. Studies typically use a ratio score of ventricular size divided by brain size (ventricular brain ratio, VBR) to control for individual variability in brain size. The lateral ventricles were found to be enlarged in most studies, but enlargement of the third ventricle in schizophrenia has been reported as well (Takahashi et al., 2006).

A second reliable finding is that patients tend to have larger sulci (i.e., the fissures between the ridges or gyri of the brain) compared to controls (Kovalev, Petrou, & Suckling, 2003). Sulcal enlargement might be independent of ventricular enlargement and could represent a different pathophysiological
process. Consistent with this notion is the suggestion that ventricular and cortical abnormalities in schizophrenia derive from different antecedents (Cannon, Mednick, & Parnas, 1989). More specifically, cortical abnormalities appear to be associated with family risk for schizophrenia (Goghari, Rehm, Carter, & MacDonald, 2007), whereas ventricular abnormalities appear more closely associated with obstetric complications (McNeil, Cantor-Graae, & Weinberger, 2000).

Third, schizophrenic patients sometimes, but not always, show abnormalities in hemispheric asymmetry. The brain normally extends farther anterior on the right and farther posterior on the left, a pattern of asymmetry described as torque. Some schizophrenia patients show a reduction, or even a reversal, of this normal cerebral asymmetry (for a review, see Malla & Payne, 2005).

**Regions of Interest**

Much of the focus in structural neuroimaging studies of schizophrenia has been on a few regions that are known to be important for cognitive performance. One such region is the frontal cortex (Salgado-Pineda et al., 2007). The results have been inconsistent, with some but not all studies reporting decreased frontal lobe volume in schizophrenia (for a review, see Zakzanis & Heinrichs, 1999). It is difficult to draw conclusions from studies of this region owing to the large size and heterogeneous nature of the frontal lobe, as well as the difficulty in identifying its boundaries. However, one new line of investigation may shed light on the issue. Premkumar and colleagues (Premkumar, Kumari, Corr, & Sharma, 2006) have recently observed that factors such as stage of illness, duration of untreated illness, and medication history affect volume. Sample differences in these factors may be contributing to the inconsistencies reported in the literature.

The findings have been more consistent for both the temporal cortex and the medial aspects of the temporal lobe. Several studies have reported reduced volume of the superior temporal gyrus in schizophrenia patients (Takahashi et al., 2006). Reduction in size of the posterior temporal gyrus appears to be related to severity of thought disorder (Subotnik, Bartzokis, Green, & Nuechterlein, 2003) and to abnormalities in an electrophysiological index of the processing of novel information (P300; McCarley et al., 1993; Meisenzahl et al., 2004).

Structural abnormalities have also been observed in subcortical areas. Researchers have found increases in the size of some regions of the basal ganglia in schizophrenia patients. In a follow-up study, first-episode patients showed an increase in the size of the caudate nuclei over an 18-month period of treatment with conventional neuroleptics (i.e., D2 antagonists), whereas control subjects showed a slight decrease in size over the same time period (Chakos et al., 1994). This finding suggests that enlarged basal ganglia structures in schizophrenia are a result of the region’s response to antipsychotic medications. However, this speculation is tentative at the present time; in a recent voxel based morphometric (VBM) study (i.e., a neuroimaging technique that allows investigation of focal differences in brain volume), researchers observed limbic system irregularities in first-episode individuals who had never been medicated (Chua et al., 2007).

There is strong evidence for reduced volume in medial temporal lobe structures, especially the hippocampus (for a recent review, see Vita, 2007). In fact, of all the regions studied, the hippocampus is one that has most consistently been identified as distinguishing people with schizophrenia from healthy controls (Schmajuk, 2001). One landmark study that illustrates this point examined MZ twins discordant for schizophrenia (Suddath, Christison, Torrey, Casanova, & Weinberger, 1990). When compared to their healthy identical co-twins, those with schizophrenia were found to have smaller temporal lobe volumes, with the hippocampal region showing the most dramatic difference between the affected and no affected co-twins. Advances in understanding of the hippocampal region have played a key role in the integration of the developmental perspective with etiological theories (a detailed example of one such model is included in a section following).

Another region of interest in schizophrenia is the thalamus (for a recent review, see Konick & Friedman, 2001). One study utilized a procedure whereby neuroanatomical differences between patients and controls were investigated by combining brain images from multiple subjects and generating an average schizophrenia brain and an average control brain (Andreasen et al., 1994). Specific regional differences between groups were observed in the thalamus and the adjacent white matter. The results were viewed within a neurocognitive framework as support for “a parsimonious explanation for the multiplicity of signs and symptoms: abnormalities in midline structures that mediate attention and information processing, particularly the thalamus and related midline circuitry” (p. 295).
Major Axis I Syndromes

Taken together, these results suggest that the thalamus is one area in which genetic factors may be significantly contributing to the illness.

Neurocognitive Correlates of Structural Abnormalities

Structural abnormalities are reliably found in schizophrenia, but what is the functional significance of these findings? Neurocognitive correlates of ventricular and sulcal enlargement have been examined using neuropsychological batteries and intellectual measures (see Antonova, Sharma, Morris, & Kumari, 2004, for a recent review). In general, ventricular and/or sulcal enlargement is predictably associated with poorer neuropsychological performance (e.g., Sanz de la Torre, Barrios, & Junque, 2005; Toulopoulou et al., 2004). Drawing more specific conclusions is difficult because the brain measures (e.g., ventricular brain ratio) are regionally nonspecific, and the neuropsychological measures are global cutoff scores. Further, deficits in more basic skills (e.g., executive function, motor coordination) are well documented in schizophrenia, and these basic skill deficits can influence performance on tests of more specific cognitive processes. Finally, antipsychotic medications, as well as medications sometimes taken to counter side effects (e.g., Cogentin), can adversely influence basic motor skills (e.g., reaction time) that are required to perform higher level cognitive tasks.

In contrast to the findings on relations between structural indexes and neuropsychological measures, which generally fall within the expected directions, the results regarding structural indexes and intellectual functioning have been mixed. Whereas the results of some studies are in the expected direction such that smaller ventricles are associated with higher IQ (Toulopoulou et al., 2004), others are in the opposite direction, and many studies did not find relationships at all (for a review, see Antonova et al., 2004). Inconsistency among the results may reflect differences in the contents of the measures of intelligence scales. For example, some subtests on standardized intelligence scales are sensitive to cognitive decline following brain injury, whereas others change very little with brain injury and are rather good indicators of premorbid ability. Overall, the pattern of results appears to depend on the type of intelligence measure. Structural abnormalities in schizophrenia seem to be associated with poor performance on subtests that are sensitive to brain injury, such as speeded tasks, but not those that reflect premorbid abilities, such as basic information and vocabulary (Antonova et al., 2004; Bilder, 1992).

Neurochemical Aspects

It has become increasingly popular to state that schizophrenia is caused by a chemical imbalance of the brain. This typically refers to an imbalance of dopamine, based on early and still influential findings. As discussed next, the dopamine hypothesis, although still maintained, is now recognized as somewhat oversimplified, and many other neurochemicals have also been implicated in the pathophysiology of schizophrenia.

In general, most current theories propose some type of functional abnormality in neurotransmission that may be a consequence (e.g., Corcoran et al., 2003; Walker & Diforio, 1997; Weinberger, 1987) or a cause (e.g., Olney & Farber, 1995) of structural brain abnormalities. As noted, a variety of neurotransmitters and neurotransmitter receptors are currently under study. Neurotransmitters are the chemicals that enable neurons to communicate with each other. A presynaptic neuron releases neurotransmitters from the vesicles in its nerve ending into the synaptic cleft. The released transmitters then interact with receptors on surrounding postsynaptic neurons. However, receptors are highly specialized and accept messages only from specific target neurochemicals. A number of factors can affect the amount of a transmitter available, including changing the amount released by the presynaptic neuron, influencing regulation in the synaptic space, or blocking receptors with other substances. Reuptake occurs when a transmitter that has been released is taken back into the presynaptic neuron. Agonists are substances that enhance neurotransmission; antagonists decrease neurotransmission.

Although a formal review is outside the scope of the present chapter, it is noteworthy that new venues of research have been aimed at delineating the effects that illicit drugs have on neurosystems and psychosis. More specifically, recent evidence suggests that the use of certain recreational drugs can also be a bioenvironmental risk factor. To the surprise of many scientists, as well as the general public, it has been shown that adolescent use of marijuana can contribute to risk for psychosis (Verdoux, Tournier, & Cougnard, 2005). Evidence to
support this relation has come from retrospective and prospective studies. Although the mechanisms involved are not yet known, there is reason to suspect that the principal active ingredient of cannabis, Δ-9-tetrahydrocannabinol (Δ-9-THC) increases risk for psychosis by augmenting dopamine neurotransmission and stress hormone release (D’Souza, et al., 2005; Viveros, Llorente, Moreno, & Marco, 2005).

Dopamine

Dopamine (DA), a monoamine, is one of the catecholamines that functions as a neurotransmitter in the human brain (Jentsch, Roth, & Taylor, 2000; Nicholls, 1994). Like epinephrine and norepinephrine, DA is synthesized from tyrosine. Although only a small proportion of neurons secrete DA, the extensive projections from these cells result in a widespread release of DA that appears to have a modulating influence on a large number of neurons. This influence can be either excitatory or inhibitory, depending on the subtype of DA receptor that is activated. The three major pathways comprising the DA system are the nigrostriatal, mesolimbic, and mesocortical. Mesocortical and mesolimbic DA neurons originate in the midbrain ventral tegmental area, whereas those in the nigrostriatal pathway originate in the substantia nigra.

The relationship between DA and psychotic symptomatology can be demonstrated by studies examining compounds such as levodopa. Levodopa increases DA transmission and is used to treat Parkinson’s. The motor abnormalities associated with Parkinson’s disease (i.e., hypokinesias, rigidity, tremors) are due to the low levels of DA that characterize the disease. However, researchers have observed that patients with Parkinson’s disease who are being treated with DA agonists (i.e., levodopa, which elevates striatal dopamine) show drug-induced hyperkinesias (the opposite series of movements from the noted hypokinesias movements related to Parkinson’s; i.e., increased involuntary movements; Hoff, van den Plas, Wagemans, & van Hilten, 2001) and, in some cases, psychotic symptomatology (Papapetropoulos & Mash, 2005). In a similar vein, researchers have observed that stimulants, such as cocaine and amphetamine, increase DA activity and can cause both hyperkinesias and psychotic symptoms (Weiner, Rabinstein, Levin, Weiner, & Shulman, 2001). The relation between DA and movement disorder is not elevated in schizophrenia patients. However, many of the results point to neurotransmitter receptor as a possible source of abnormal DA activity in schizophrenia.

These and other reports fostered a large number of investigations aimed at determining whether elevated fluid levels of DA or DA metabolites characterized schizophrenia patients (e.g., homovanillic acid; HVA). Lieberman and Koreen (1993) provided a systematic review of these studies and suggested that, taken together, the results offer little support for heightened DA levels in schizophrenia. Plasma HVA, which partially reflects brain DA turnover, is not elevated in schizophrenia patients. However, many of the results point to neurotransmitter receptors as a possible source of abnormal DA activity in schizophrenia.

Advances in neuroscience have led to the identification of multiple subtypes of DA receptors. To date, two general classes of DA receptors have been...
localized in the human brain: D1 and D2 (Nicholls, 1994; included in the D1 “family” are D1 and D5, whereas the D2 family includes D2, D3, and D4). The distinction between these two subtypes of receptors is based on the fact that the D1 subtype of receptor is positively coupled with adenylyl cyclase activation, whereas the D2 subtype inhibits adenylyl cyclase. D1 receptors are more common than D2 receptors but have a lower affinity for DA.

It has been shown that the D2 subtype of DA receptor is a primary target of typical and atypical antipsychotics (Busatto et al., 1995; Carlsson, 1995). In an effort to test the hypothesis of DA receptor abnormalities in schizophrenia, several research groups have examined postmortem brain tissue from patients (e.g., Reynolds & Czudek, 1988; Toru et al., 1988). The results of these studies suggested an increase in the densities of D2, but not D1, receptors in subcortical regions, particularly the basal ganglia (Kestler, Walker, & Vega, 2001). The findings were mitigated, however, by the fact that many of the brain samples had been obtained from patients who were advanced in age and had received long-term treatment with antipsychotic drugs (Andreasen et al., 1988). Exposure to antipsychotics was considered relevant because some animal studies had revealed that D2 receptor density was increased by drug exposure.

Positron emission tomography (PET) technology (a neuroimaging procedure assessing brain function) has provided a means for studying the characteristics of neurotransmitter receptors in vivo, thus allowing investigators to focus on younger patients with no or shorter antipsychotic drug exposure. The findings from this research have not clarified the issue, however, because some studies of drug-naive patients showed elevated D2 receptor densities whereas others did not. (For reviews, see Andreasen et al., 1988; Kestler et al., 2001; Tune et al., 1993.) The inconsistent findings have generated spirited debates about the influence of various methodological differences (e.g., use of different radioligands and/or receptor quantification procedures) on the study outcomes (Wong, 1992), but there has been no resolution to the DA receptor density controversy.

Several investigators have proposed that it is the ratio of DA receptor subtypes that is abnormal in schizophrenia, rather than the absolute density of a single subtype (Joyce, Lexow, Bird, & Winokur, 1988). Specifically, it has been proposed that schizophrenia is associated with an increased ratio of D2 to D1 receptors. Given the evidence that there are complex synergistic and antagonistic interactions among DA receptor subtypes, this hypothesis seems plausible.

Finally, it should be noted that studies of normal subjects have indicated that DA may be related to attention and memory (cf. Keefe & Harvey, 1994). Because schizophrenic patients have been extensively shown to display deficits in these functions, there may be an association between abnormal DA levels and impaired cognition in schizophrenia.

**Norepinephrine**

As noted, norepinephrine (NE) and DA originate from the same synthetic pathway. Lieberman and Koreen (1993) have pointed out that empirical data linking NE with schizophrenia are limited. Nonetheless, there are several reports of a relation between NE and symptom severity. This is not surprising in light of the biochemical association between NE and DA. Also consistent with the hypothesis that NE is involved in schizophrenia are findings that atypical antipsychotics reduce NE activity (Lieberman, 1994; Yamamoto & Hornykiewicz, 2004).

**Amino Acids**

The amino acids—glutamate, y-aminobutyrate (GABA), and glycine—act as neurotransmitters at a large proportion of CNS synapses. Glutamate is an excitatory neurotransmitter. Most projecting glutamatergic pathways originate in the neocortex and the hippocampus; they connect the hippocampus, the prefrontal cortex, and the thalamus (all regions highly implicated in schizophrenia). Glutamate is also a major neurotransmitter for interneurons that modulate neurotransmission within brain regions. Within the past decade, researchers have turned their attention to glutamate as a neurochemical factor in schizophrenia (Carlsson, Hansson, Waters, & Carlsson, 1999; Goff & Coyle, 2001; Tsai & Coyle, 2002).

Olney and Farber (1995) proposed that a specific subtype of glutamate receptor, the N-methyl-d-aspartate (NMDA) receptor, is hypofunctional in schizophrenia patients. They based this hypothesis on several research findings. It has been shown that phencyclidine (PCP), which blocks the ion channel of the NMDA receptor, produces a psychotic syndrome that involves both positive and negative
symptoms. Further, NMDA antagonists have been shown to cause degeneration of neocortical and limbic regions (e.g., anterior cingulate, parietal, temporal, and entorhinal cortex, hippocampus, and amygdala) in the rat brain. These are the same regions that are reported to be abnormal in studies of schizophrenia patients. More recently, researchers have found evidence of diminished activity at glutamatergic receptors among schizophrenia patients (Tsai & Coyle, 2002). Finally, the neurotoxic effects of NMDA receptor antagonism can be blocked by typical and atypical antipsychotics.

Olney and Farber (1995) have also noted that their NMDA receptor hypofunction hypothesis is compatible with DA theories of schizophrenia, in that DA receptor hyperactivity can result in the inhibition of glutamate release and a consequent hypofunction of NMDA receptors. Thus, NMDA hypofunction might be the primary defect in some cases of schizophrenia, whereas in other patients it might be a secondary consequence of DA overactivity. Other authors have also cited the interaction between glutamate and DA as a factor in schizophrenia (Iverson, 1995; Wan, Geyer, & Swerdlow, 1995).

GABA is the main inhibitory neurotransmitter in the cortex, and GABA cells are predominantly interneurons (neurons that are exclusively connected with other neurons rather than sensory cells or muscles; interneurons process signals from one or more sensory neurons and relay signals to motor neurons). Benes (1995) has proposed that a decrease in GABAergic activity, specifically decreased GABAergic innervation of frontal cortex, might be involved in schizophrenia. In support of this theory, the uptake and release of GABA has been shown to be abnormal in some studies of postmortem brain tissue from schizophrenia patients (Lewis, Pierrri, Volk, Melchitzy, & Woo, 1999). In addition, researchers have observed abnormalities in the interconnections among GABA neurons (Benes & Beretta, 2001). GABA interneurons (nonpyramidal neurons) are the most common interneurons, and they act to inhibit pyramidal neurons in the cortex. Benes hypothesized a loss of these inhibitory GABA interneurons in the anterior cingulate cortex. This, in turn, produces an upregulation of GABA receptors on pyramidal neurons. In support of this hypothesis, Benes has reported the results of postmortem studies that show an increase in GABA receptor binding on neurons in layers II and III of the cortex in schizophrenia patients.

**Serotonin**

Serotonin (5-HT) is a monoamine that is synthesized from tryptophan and originates in cell bodies located in the raphine nuclei that project to the cortex, striatum, and cerebellum. Several theorists have suggested that schizophrenia may involve excess activity of 5-HT pathways (Carpenter, 1995; Huttenen, 1995; Meltzer, 1991).

Serotonin (5-HT) was originally implicated in schizophrenia because certain psychotomimetic drugs, such as LSD, enhance 5-HT activity. This, in turn, can produce perceptual and ideational distortions similar to the symptoms of schizophrenia (hence the term *psychometric*). Studies of 5-HT levels in schizophrenia patients have yielded inconsistent results, with some showing elevations and others showing no difference between patients and normal controls (for a review, see Lieberman & Koreen, 1993).

More recently, hypotheses about 5-HT have been based on findings from studies of new antipsychotic agents (Tyson, Laws, Flowers, Tyson, & Mortimer, 2006). These and other findings have led to renewed speculation about the role of serotonin in the production of psychotic symptoms. There is recent evidence that certain types of 5-HT (5-HT1) receptors are elevated in schizophrenia, while others (5-HT2) are decreased (Arora & Meltzer, 1991; Lopez-Figueroa et al., 2004). Thus serotonergic receptor abnormalities may confer a heightened sensitivity to 5-HT activity in schizophrenia. Meltzer and Nash (1991) have cited evidence that 5-HT has an inhibitory effect on DA activity in the nigrostriatal pathway, thus explaining the lowered risk for extrapyramidal side effects with atypical antipsychotics.

**Adrenal Steroids**

As discussed earlier, the diathesis-stress model of schizophrenia continues to be the dominant conceptual framework in the literature on schizophrenia. The hypothalamic-pituitary-adrenal (HPA) axis is one of the major neural systems mediating the stress response in humans. Following stressful events, a cascade of neurochemical processes culminates in the release of adrenal steroids, most notably cortisol, in human and nonhuman primates.

It has recently been proposed that cortisol may play a potentiating role in the expression of abnormalities in dopaminergic and glutamatergic neurotransmission. As Walker and Diforio (1997) point out, evidence for this comes from several areas of
investigation. First, schizophrenia patients show heightened baseline cortisol when compared to normal controls (Mitropoulou et al., 2004). Second, the hippocampus, which plays a central role in the modulation of the HPA axis, shows reduced volume in schizophrenia patients (Baare et al., 2001; Suddath et al., 1990). Research on nonschizophrenia subjects has shown that hippocampal volume is inversely correlated with cortisol levels (Hibberd, Yau, & Seckl, 2000). Finally, cortisol acts to enhance DA activity, and recent reports indicate that prenatal exposure to stress hormones may also increase DA receptor density (Coe et al., 2003). This suggests a neural basis for the demonstrated effects of psychosocial stress exposure on schizophrenia symptoms.

**Neural Circuits**

As data have accumulated from the postmortem and neuroimaging studies described above, it has become apparent that a broad range of brain abnormalities is associated with schizophrenia. Many of these abnormalities, particularly reductions in gross and regional volumes and enlargement of the ventricles, have been observed in other disorders, both neurological and psychiatric. Thus, these abnormalities may not reflect the critical neuropathologic feature in schizophrenia. They may, instead, represent secondary consequences of the same CNS insult that conferred the neural liability for schizophrenia.

**Neurodevelopmental Models of Schizophrenia**

As noted earlier, Kraepelin believed that schizophrenia was an early form of dementia (i.e., dementia praecox) that followed a degenerative course. As a result, for many years, the predominant view of schizophrenia has been that it starts in young adulthood and then becomes progressively worse over time. However, the more recent neurochemical and neuroimaging findings, as well as clinical observations that most patients with schizophrenia do not show the progressive deterioration characteristic of the dementias and that some patients do improve over time, have led to an alternate notion: that schizophrenia is a neurodevelopmental disorder. According to the latter view, the basic biological error leading to schizophrenia occurs very early in development (in many cases, prenatally), is triggered during late adolescence/early adulthood, and may not involve further major deterioration in brain functioning after the initial symptoms have appeared.

For example, neuroanatomical abnormalities in schizophrenia were initially considered to be evidence of brain atrophy, partly because the types of abnormalities (ventricular and sulcal enlargement) are seen in known degenerative disorders. However, structural abnormalities have also been found in untreated, first-episode patients, indicating that long illness and medications were not necessary for their occurrence. Also, studies have generally failed to find evidence of reactive gliosis, the process in mature brains that occurs in response to cell destruction, suggesting that structural changes most likely occurred in an immature brain, long before the onset of illness.

Another way to examine the neurodevelopmental versus neurodegenerative distinction is through longitudinal studies of repeated brain scans to determine whether ventricular enlargement progresses over time. Most studies have not found any progression of the abnormalities, but a few studies reported an increase in ventricular size over time (Bilder, 1992; Price et al., 2006). The evidence is generally consistent with the view that structural abnormalities in schizophrenia largely reflect neurodevelopmental factors instead of neurodegenerative factors (e.g., atrophy). In some cases, both developmental and deteriorative factors could be operating in the same individual. Neurodevelopmental processes might explain the majority of the structural abnormalities, with some additional changes occurring after onset of illness. Nevertheless, from the neurodevelopmental perspective, the major brain abnormalities appear to have developed by illness onset. Interest in the neurodevelopmental view of schizophrenia has been steadily gathering momentum (e.g., Cannon et al., 1994; Corcoran et al., 2003; Grace, 2007; Jones & Murray, 1991; Murray et al., 1992; Walker & Diforio, 1997; Weinberger, 1986, 1987). Weinberger suggested that there can be numerous causes of the lesion, including heredity and various environmental insults, such as injury, infection, or immunologic disorder, and that different causes may lead to varying levels of pathology and thus clinical severity.

Considerable recent evidence of developmental abnormalities on the cellular level has been reported that can account for this type of neurodevelopmental process (Jones & Murray, 1991; Murray et al.,
1992; Weinberger, 1986, 1987). Some examples include abnormal synaptic pruning, axonal myelation, and defects in embryonic cell migration (Falkai, Bogerts, & Rozumek, 1988; Jakob & Beckmann, 1986; Kovelman & Scheibel, 1984; Spear, 2003). As pointed out by several researchers, since the myelination of axons continues well into adolescence, this particular abnormality could directly relate to the delayed clinical expression of schizophrenia.

There are numerous developmental changes in the CNS during puberty and early adulthood. Feinberg (1982) pointed out that adolescence is marked by a dramatic acceleration in synaptic pruning, a process that culminates in the elimination of some synapses. For example, the adolescent period rivals that of newborns; at the end of puberty, the brain will have half of the average number of synapses per cortical neuron that it held prior to puberty (Spear, 2003). The end result of pruning is presumed to be more efficient neural functioning, owing to the elimination of redundant or nonessential neural connections. Feinberg suggested that excessive or insufficient pruning might result in aberrant interconnections that lead to psychotic symptoms. Along these same lines, Benes (1994, 1995) has shown that myelination of certain limbic pathways extends into early adulthood in normal subjects. She has suggested that an abnormality in the myelination of limbic pathways may play a role in the emergence of the cognitive and affective signs of schizophrenia.

A Simplified Neurodevelopmental Model

The neurodevelopmental view of schizophrenia, within a diathesis-stress framework, underlies high-risk research, an area concerned with identifying “biobehavioral markers” of the genetic predisposition to schizophrenia and then using these markers to intervene and, it is hoped, prevent the expression of the schizophrenia illness (these markers are discussed below). A simplified version of this type of model is presented in Figure 12.2.

The starting point of the model is with a genetic vulnerability, some type of environmental insult, or both, that occurs very early in development and leads to a biological susceptibility to schizophrenia. A number of possible causative factors are discussed above in the section on etiology.

The pathway shown on the figure represents the development of the schizophrenia diathesis, beginning with the earliest etiological factors and ending with the clinical expression. A critical aspect, following Weinberger and others, is that although the underlying pathophysiology causing the susceptibility (sometimes referred to as the “lesion”) occurs early in development, behavior does not become affected until much later. The lesion remains dormant until triggered by some developmental event, at which point the clinical symptoms start to emerge. Findings from high-risk research indicate that, in contrast to clinical symptoms, subtle neurocognitive deficits such as impaired attention appear to be present throughout development, but are observable only when measured using highly sensitive procedures.

It is assumed that susceptibility can take the form of one or more basic brain abnormalities, either structural, functional, or biochemical. Earlier parts of this chapter have presented some possibilities. For example, structural abnormalities may include enlarged ventricles or reduced temporal lobes; abnormal DA levels are a well-established biochemical abnormality. Although not discussed in detail here, there is also considerable evidence from PET and functional MRI studies suggesting functional impairments...
of the brain in schizophrenia. Weinberger and his colleagues (e.g., Weinberger & Berman, 1988) have reported hypofrontality (i.e., underactivity of the frontal lobes), especially in the dorsolateral prefrontal cortex. In addition, several lines of research suggest that prenatal insult can produce hippocampal damage in the fetus, and this can render the organism hypersensitive to stress postnatally (Szuran, Pliska, Pokorny, & Welzl 2000). Thus the hippocampal abnormalities observed in schizophrenia patients may contribute to stress sensitivity.

The brain abnormalities are, in turn, thought to be associated with a variety of neurocognitive deficits, that is, biobehavioral markers. Such markers differ from the molecular genetic markers discussed earlier. Biobehavioral markers provide no information about the location of a disease gene. Instead, they indicate the presence of the biological susceptibility for schizophrenia and provide information about the pathophysiology of the disorder.

The neurocognitive deficits are labeled biobehavioral because they are viewed as intermediate between basic brain functions (the bio) and more complex clinical features of the illness (the behavioral). They consist of such things as the ability to process information in the environment (i.e., attention) or to move the eyes smoothly when tracking a moving target. Because they are behavioral abnormalities, they are phenotypic (as opposed to genetic) markers. The markers part of the label refers to the notion that, if valid, the deficits signal or mark the presence of the biological susceptibility to schizophrenia.

The model pathway also illustrates another critical assumption. The cognitive marker deficits can be detected many years before clinical symptoms begin to emerge. These markers can therefore serve as predictors of future illness, paving the way for intervention programs. That is, once validated, markers can be used to identify susceptible individuals. This will provide a way to screen at-risk and other populations for individuals most in need of intervention. In addition, because the marker deficits are thought to be involved in the pathophysiology of schizophrenia, they may point to effective interventions. The goal of such programs is to interrupt the developmental pathway and to eliminate or minimize the clinical expression of illness.

As can be seen in the model, stressors come into play at various points along the developmental pathway of the diathesis. These can be biological (e.g., intrauterine trauma, viral exposure, severe malnutrition, birth complications) or psychosocial (e.g., psychosocial or interpersonal disruptions). However, aspects of the environment considered stressful (especially psychosocial, interpersonal) might not be particularly stressful in a normative sense. Rather, “persons who are predisposed to schizophrenia may develop the illness not because of exposure to excessive stress but because they are not protected from normal levels of stress” (Keefe & Harvey, 1994, p. 99).

It is clear that any model must explain why the onset of schizophrenia typically occurs in late adolescence/early adulthood. There are numerous developmental changes in the CNS system during puberty and early adulthood, and our recent understanding of the interplay between neuroendocrine function and neurotransmission contributed to integrating developmental complexities into the present model.

As noted, there is evidence that some cases of psychotic disorders involve an abnormality in striatal DA receptors, in either the regional distribution, density, affinity, subtype ration, or an interaction that results in a heightened sensitivity to DA (Walker 1994; Walker & Diforio, 1997). In turn, this biological diathesis can be moderated by the HPA axis due to the augmenting effects of cortisol on DA activity. The gradual normative increase in HPA activity throughout adolescence (Kiess et al, 1995; Walker, Walder, & Reynolds, 2001) may trigger this cycle in vulnerable individuals (e.g., hippocampal abnormality, striatal abnormality, innervated DA pathways).

In other words, during adolescence, normatively elevated cortisol might interact with a vulnerability thus augmenting DA (expressing itself as behavior problems, prodromal symptoms, or eventually Axis I psychotic disorder). This augmented DA reciprocally affects cortisol levels, thus heightening stress responsivity. These biological mechanisms collectively result in a stress cascade and in the clinical expression of the individual’s constitutional vulnerability to psychosis (Corcoran et al., 2003; Walker & Diforio, 1997).

This phenomenon, in part, can explain the escalating behavior problems observed in preschizophrenic participants and the modal age at onset of the prodrome (i.e., period prior to onset of Axis I psychosis, which is characterized by decreased social and role functioning and subthreshold psychotic symptoms), late adolescence (Neumann, Grimes, Walker, & Baum, 1995). Whether DA overactivation is the primary abnormality in schizophrenia or a secondary (i.e., downstream) consequence of
other factors, activation of the HPA axis is a moderator between stress and symptom exacerbation. Stressors are associated with long-lasting effects on mesolimbic DA and the HPA axis in humans, augmenting DA release in the ventral striatum, which is correlated to the magnitude of the salivary cortisol response, suggesting a reinforcing effect of cortisol on the dopaminergic system (Oswald et al., 2005). Overactivity of both the HPA axis and DA systems in psychotic thinking in psychotic major depression substantiates the roles of the HPA axis and central DA dysregulation in its etiology. Taken together, this suggests that differences in HPA axis function may influence vulnerability to disorders associated with dysregulated DA, such as schizophrenia.

Note that the diathesis can have a number of alternate expressions, ranging from the full-blown illness through a number of less severe variants (e.g., personality disorders or schizophrenia-related features) to no behavioral expression. Several researchers have proposed that the diathesis is most likely to be expressed clinically in the form of a nonpsychotic, schizotypal-like personality disorder, with some type of environmental stressor required to trigger psychosis (e.g., Cannon & Mednick, 1993; Cannon et al., 1994; Siever et al., 1990). It is further assumed that additional factors (environmental, biological, cognitive, personality) can serve as moderators, either exacerbating or reducing the severity of the expressed illness.

Applying the Neurodevelopmental Approach: High-Risk Research

A neurodevelopmental view of schizophrenia is the foundation of high-risk research.

Because the risk for schizophrenia in the general population is about 1%, if 1,000 youngsters were randomly selected and then closely followed for, say, 25 years, only about 10 subjects could be expected to develop schizophrenia. Consequently, researchers have turned to a population with higher than average risk for developing schizophrenia—the offspring of schizophrenic parents, who are about 12 times as likely to become ill as members of the general population (see Figure 12.1).

Pearson and Kley (1957) were the first to recognize the advantages of a prospective design that involved the offspring of schizophrenic parents. Their proposal was followed by the pioneering work of Mednick, who, in 1962, initiated the first offspring high-risk study on a large scale (Mednick & McNeil, 1968; Mednick & Schulsinger, 1968), and then by several additional high-risk studies that were begun between the late 1960s and early 1970s. These have been referred to as the “first generation” of high-risk (HR) studies. Since this time, several ongoing prospective studies following high-risk youth continue to make valuable contributions to clinical understanding of the development of schizophrenia (e.g., see Mittal, Tessner, et al., 2007).

The Prodrome The majority of individuals who succumb to schizophrenia and other psychotic disorders manifest prodromal signs of behavioral disturbance (Larsen, McGlashan, Johannessen, & Vibe-Hansen, 1996). These signs often begin in early adolescence and become progressively worse as the individual approaches young adulthood (Cornblatt, Lencz, & Obuchowski, 2002). It is estimated that at least 70% of preschizophrenic people manifest behavioral dysfunction during adolescence (Cannon, Rosso, Bearden, Sanchez, & Hadley, 1999; Neumann, Grimes, Walker, & Baum, 1995), with many showing schizotypal signs, such as social withdrawal and thought abnormalities (Walker, Baum, & Diforio, 1998), deficits in memory and executive function (Silverstein, Mavrolefteros, & Turnbull, 2003), and neurological soft signs (Neumann & Walker, 2003). It is assumed that the heightened risk associated with this developmental period results, in part, from neuromaturational processes that trigger the behavioral manifestation of latent vulnerability (Walker & Diforio, 1997).

The prodromal period represents both a viable point for intervention, and a developmental period with high potential to shed light on the etiology of schizophrenia. Because schizotypal signs are a common manifestation of the schizophrenia prodrome (Cornblatt et al., 2002), research in this area has accelerated in recent years. A series of ongoing longitudinal studies, designed to follow schizotypal adolescents through the schizophrenia risk period, holds promise for elucidating etiology, increasing the complexity of developmental understanding, and highlighting viable risk markers that may enable preventive intervention.

Preventive Intervention and a Developmental Neural Diathesis-Stress Model Because biological markers are relatively easy to detect, and are now suspected to predict factors associated with a poor course of illness among those individuals with high risk for developing psychotic disorders (i.e., schizotypal adolescents or schizophrenia offspring), such signs can serve as a valuable marker for the highest of the
high-risk individuals (an ultra high risk) and minimize false positives in prediction. Because there are numerous concerns with medicating youngsters with antipsychotic medications, blanket medication of all high-risk individuals is not practical. Thus, identifying factors that can enhance prediction of the subgroup that can benefit from preventive treatment is rapidly becoming a priority.

The importance of this objective is highlighted by evidence that longer duration of untreated psychotic illness is associated with a poorer course of illness. These data suggest that treating youngsters at high risk for developing psychotic disorders is a potentially effective prophylactic intervention strategy. Thus, investigation of biomarkers represents a critical step in this process: integrating empirical data with theory to inform practice.

Summary

Understanding schizophrenia remains a formidable task. However, recent developments throughout the schizophrenia research literature suggest that progress is being made. First, in terms of etiology, sophisticated molecular genetic techniques are offering great hope for finding the genes underlying complex illnesses. Furthermore, adding biobehavioral markers to these analyses may facilitate linkage studies of schizophrenia. Second, with regard to pathophysiology, technological advances in brain imaging are improving opportunities for examining brain function, structure, and chemistry. This may result in the identification of the neural abnormalities leading to schizophrenia. Third, recent integrations of neuroscience, genetics, and the developmental perspective, have enhanced appreciation of the complexity of etiology, course, and treatment. Finally, the study of cognitive mechanisms, motor functions, and other biomarkers promises to provide early predictors of the impending illness. This, in turn, will pave the way to feasible intervention programs. Researchers are thus coming closer to an understanding of the causes of schizophrenia, the pathways to illness, and, we hope, how to prevent or at least better treat it.

Electronic References

http://www.schizophrenia.com/sznews/archives/003407.html
http://www4.od.nih.gov/ofm/diseases/index.stm

References


Development and Psychopathology, 6, 723–739.


Schizophrenia: Etiology and Neurocognition


middle and inferior temporal gyri. Schizophrenia Research, 87(1-3), 116–126.


Webb, C. T., & Levinson, D. F. (1993). Schizotypal and paranoid personality disorder in the relatives of patients with schizophrenia and...


