62

Disorders of Thought and Volition: Schizophrenia

The success of neurobiology in providing insights into perception, cognition, and more recently emotion has inspired increasingly sophisticated biological investigations into disorders of thought and mood. In this chapter and the next we examine the four most serious disorders of thinking and mood: schizophrenia, depression, mania, and the anxiety states. These disorders involve disturbances in thought, self-awareness, perception, affect, volition, and social interaction.

In addition to being scientifically challenging, mental illness such as schizophrenia is of great social importance. Tragically this illness results in lifelong disability. The World Health Organization counts schizophrenia as one of the most significant contributors to disease burden (defined as healthy years of life lost to illness) worldwide. Fully 5% of people with schizophrenia commit suicide. Many more are homeless. The vast majority are unable to function successfully in school or in the workplace. Before the advent of psychopharmacologic therapies, schizophrenia and the mood disorders accounted for more than half of all hospital admissions in the United States. Even now schizophrenia accounts for approximately 30% of all hospitalizations.

The pattern of symptoms of schizophrenia are remarkably similar in all countries and cultures. The average prevalence worldwide ranges between 0.5 and 1%; the male-female ratio is 1.4:1. Diagnosis is usually made during late adolescence or early adulthood with the emergence of full symptoms, but in retrospect the illness begins far earlier with prodromal symptoms.

Diagnosis of Schizophrenia Is Based on Standardized Clinical Criteria

In medicine the understanding of a disease, and therefore its diagnosis, is ultimately based on identification of (1) etiological factors (such as microbes, toxins, or genetic risks) and (2) pathogenesis (mechanisms by which etiologic agents produce disease). Unfortunately, the etiology and pathogenesis of most mental disorders have not been determined. As a result, psychiatric diagnoses still rely on the patient's description of symptoms, the examiner's observations, a detailed natural history (the course of the illness over time), and the response to treatment.

This approach to psychiatric diagnosis began at the turn of the 20th century with the work of Emil Kraepelin in Germany. Influenced by Rudolf Virchow, the German pioneer of cellular pathology, and by Thomas Sydenham, the English clinician who focused attention on the natural history of medical diseases, Kraepelin studied mental disorders as specific disease processes. Even without knowledge about the etiology and pathogenesis, of diseases affecting thought, emotion, and behavior, he argued, such diseases could still be distinguished on the basis of signs, symptoms, and natural history.

Of course, the presentation of a single sign or symptom is not in itself evidence for disease because it may occur in healthy people. But when certain signs and symptoms occur together they form a syndrome, a condition that can be distinguished from normal behavior or from other clusters of signs and symptoms. The natural history of a disease is studied by tracing the onset of signs and symptoms in patients' lives and how they change with time. Thus a syndrome can emerge at a characteristic age or it can follow a characteristic clinical course. For example, Kraepelin recognized that most patients with schizophrenia (which he called dementia praecox) do not recover the level of functioning they had prior to the onset of the disease, whereas most patients with mood disorders experience cycles of relapse and at least partial recovery.

Since the 1980s the diagnosis of psychiatric disorders has been based on standardized criteria that have made diagnosis more reliable. Two different clinicians applying standardized criteria for schizophrenia are very likely to arrive at the same diagnosis. Nevertheless, without etiological or pathophysiological data and lacking objective tests, current diagnostic systems such as the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (*DSM-IV*) of the American Psychiatric Association cannot define disease states in scientifically verifiable terms. With progress in such areas as genetics and neuroimaging, it eventually should be possible to arrive at objectively verifiable and thus valid diagnostic criteria for mental disorders.

The Symptoms of Schizophrenia Can Be Grouped into Positive, Negative, and Cognitive

It is useful to subdivide the symptoms of schizophrenia into three clusters because each may reflect different aspects of the pathophysiology and because each responds differently to the medications presently used. Positive or psychotic symptoms include mental phenomena that do not occur in healthy people, such as hallucinations and delusions. Negative (or "deficit") symptoms result from impairment of normal functions and can include blunted emotional responses, withdrawal from social interactions, impoverished content of thought and speech (Box 62–1), and a lack of motivation.

A third symptom cluster includes cognitive abnormalities—sometimes described as "disorganization symptoms." These symptoms impair working memory and executive functions—the ability to organize one's life. These cognitive symptoms typically persist even during otherwise successful treatment with medication and are thought to be significant contributors to long-term disability. Interestingly, cognitive symptoms can be found to some degree in persons at very high risk of developing schizophrenia but who have not yet experienced hallucinations or delusions, and in otherwise healthy relatives of patients with schizophrenia, suggesting that cognitive symptoms reflect genetic predispositions to schizophrenia.

The medications used to treat schizophrenia are called antipsychotic drugs and are most effective at diminishing the positive symptoms as well as psychotic symptoms that occur in mood disorders. None of the medications reliably benefits the cognitive symptoms.

Schizophrenia Is Characterized by Psychotic Episodes

The most dramatic manifestations of schizophrenia are psychotic symptoms, including hallucinations and delusions. Hallucinations are percepts that occur in the absence of appropriate sensory stimuli and can occur in any sensory modality. In schizophrenia the most common hallucinations are auditory. Typically, a patient hears voices, but noises or music are also common. Sometimes the voices will carry on a dialog and frequently are experienced as bullying and derogatory. Occasionally, voices will issue commands to the patient that can create a high risk of harm, including suicide. Neuroimaging studies of subjects experiencing auditory hallucinations suggest that areas normally involved in the processing of language are recruited during hallucinations. These include Broca's area in the frontal lobe and Wernicke's area in the superior temporal lobe of the cerebral cortex (see Chapter 60).

Delusions are firm beliefs that are not realistic and not explained by the patient's culture. They can be so powerful that sufferers cannot (or refuse to) compare their beliefs to what is actually happening in the world. Delusions can be quite varied in form. For some patients reality is distorted: The world is full of hidden signs meant only for them (delusions of reference), or they are being closely watched or persecuted (paranoid

Box 62–1 Schizophrenic Speech

Language disturbance is a central feature of schizophrenia and one of the primary behaviors by which it is diagnosed. Grammar is reasonably intact, but content can wander or be incoherent, a symptom that is commonly referred to as "loosening of associations." More bizarre but less common patterns of speech include neologisms (idiosyncratically invented words), blocking (sudden spontaneous interruptions), or clanging (associations based on the sounds rather than the meanings of words, such as "If you can make sense out of nonsense, well, have fun. I'm trying to make cents out of sense. I'm not making cents anymore. I have to make dollars.")

Examples of loosening of associations are:

"I'm supposed to be making a film, but I don't know what is going to be the end of it. Jesus Christ is writing a book about me."

"I don't think they care for me because two million camels . . . 10 million taxis . . . Father Christmas on the rebound."

Question: "How does your head feel?" Answer: "My head, well that's the hardest part of the job. My memory is just as good as the next working man's. I tell you what my trouble is, I can't read. You can't learn anything if you can't read or write properly. You can't pick up a nice book, I don't just mean a sex book, a book about literature or about history or something like that. You can't pick up and read it and find things out for yourself."

Several different types of loosening of associations have been proposed (such as derailment, incoherence, tangentiality, or loss of goal). However, it remains unclear whether these reflect disturbances in fundamentally different mechanisms or different manifestations of a common underlying disturbance, such as the inability to represent a "speech plan" to guide coherent speech. A disturbance of such a mechanism would be consistent with, and may parallel, impairment of control of other cognitive functions in schizophrenia, such as deficits in working memory.

delusions). Others experience bizarre delusions, for example that some entity is inserting or extracting thoughts from their brain or that their dental fillings are radio transmitters broadcasting what they say to nefarious groups. Psychotic symptoms can also occur in mood disorders and drug-induced delirium, but the other symptoms and clinical course of those states are not consistent with schizophrenia.

The full emergence of schizophrenia is often preceded by a period of early symptoms. In this prodromal period the patient can behave eccentrically, become socially isolated, exhibit blunted affect, poverty of speech, a poor attention span, and lack of motivation. Once the disease is fully manifest, periods of florid psychosis typically occur, accompanied by markedly disordered thinking and abnormalities in the regulation of emotion. These periods of overt psychosis are interspersed with periods of residual symptoms. After the first few episodes the patient rarely returns to full normal functioning.

Both Genetic and Nongenetic Risk Factors Contribute to Schizophrenia

Schizophrenia, like many other mental illnesses, runs in families. As early as 1930 Franz Kalman in Germany studied familial patterns of transmission and concluded that genes contribute significantly to schizophrenia. Three major strategies have been used to quantify the contribution of heredity to the risk of schizophrenia and to understand how genetic risk is transmitted.

In one strategy the rate of concordance for schizophrenia in monozygotic twin pairs, whose DNA sequences are 100% identical, is compared with that in dizygotic twin pairs, whose DNA sequences are on average 50% identical. Assuming that the familial environment is roughly identical for both types of twin pairs, then if genes play a significant role the concordance rates should be higher among monozygotic pairs than among dizygotic pairs. In fact, monozygotic twins have a concordance rate of nearly 50% for schizophrenia, whereas dizygotic twins have a concordance rate of approximately 15% (slightly higher than that for ordinary siblings, which also have on average 50% genetic identity).

Although these rates suggest an important role for genes in schizophrenia, they also demonstrate that genes are not completely determinative. If they were, the concordance rate for monozygotic twins would be 100% as it is in Huntington disease for example. Thus factors other than inherited DNA sequence, such as new mutations, epigenetic modification of DNA,

environmental factors, and stochastic factors occurring during brain development, play a role in converting inherited genetic vulnerability into the disease.

To separate genetic factors and environmental influences more clearly, Seymour Kety, David Rosenthal, and Paul Wender examined children who were adopted at or shortly after birth in Denmark, a country where very accurate family and health records are kept. They found that the rate of schizophrenia in the biological family of an adoptee was much more strongly predictive of schizophrenia than the rate in the adoptive family. Kety and his colleagues also observed that some of the blood relatives of schizophrenic adoptees exhibited some symptoms of schizophrenia, such as social isolation, suspiciousness, eccentric beliefs, and magical thinking, even though they did not have full-blown schizophrenia. These symptoms are part of what is now called schizotypal personality disorder. Kety and his colleagues did not possess modern understandings of working memory, but it would have been interesting to know whether their sample also exhibited the cognitive abnormalities now documented in some relatives of people with schizophrenia. Overall the schizotypal symptoms are thought to be a mild, nonpsychotic form of the disease.

More recently, unaffected monozygotic twins and even siblings of patients with schizophrenia have been found to exhibit some neuroanatomic abnormalities similar to those with the disease. In one magnetic resonance imaging (MRI) study monozygotic twins discordant for schizophrenia had similar deficits in the dorsolateral prefrontal cortex and superior temporal gyrus.

Studies by Irving Gottesman of extended pedigrees of Danish patients with schizophrenia also support the importance of genes. Gottesman noted the correlations between the risk of schizophrenia in relatives and the percentage of the total genetic material each relative shared with the patient. He found a greater lifetime risk of schizophrenia among first-degree relatives (parents, siblings, and children, who share 50% of the relatives' DNA sequences) than among second-degree relatives (aunts, uncles, nieces, nephews, and grandchildren), who share 25% of their DNA sequences with the patient. Even third-degree relatives (who share only 12.5% of the patient's DNA sequences) were at higher risk for schizophrenia than the 1% of the population at risk for this disease (Figure 62–1).

With the advent of modern genomic technologies during the last decade, progress has been made in identifying variations in DNA sequence that contribute to the risk of schizophrenia. As with many common disorders, risk for schizophrenia has proven to be genetically heterogeneous, with no single gene proving necessary or sufficient. Two forms of genetic variation have been associated with schizophrenia: Variations in single nucleotide bases, and larger chromosomal deletions, duplications, or translocations. In most cases schizophrenia appears to result from the action of a large number of genes together with environmental risk

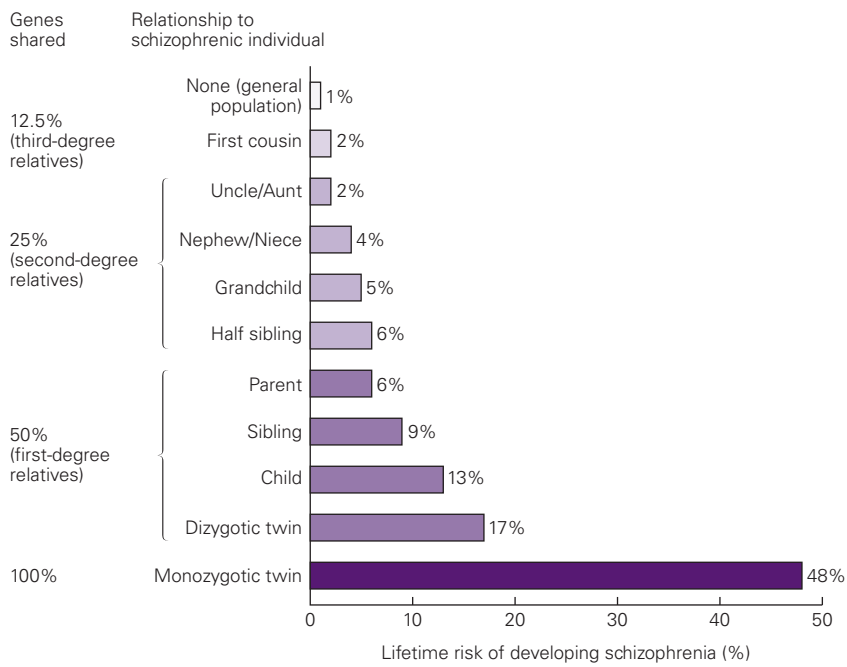


Figure 62–1 Lifetime risk of schizophrenia as a function of genetic relatedness to a person with schizophrenia. Note that risk increases with increased genetic relatedness but varies within categories of relatedness, reflecting epigenetic effects or new mutations. (Reproduced, with permission, from Gottesman 1991.)

factors. In a minority of cases schizophrenia risk is markedly elevated by chromosomal abnormalities such as a microdeletion on chromosome 22q11.2.

As with any genetically influenced disease, understanding how certain sequences at particular loci in the genome confer risk should provide important clues to pathophysiology, and thus treatment development. Because schizophrenia may result from abnormal developmental processes in the brain, knowing the time during development and adulthood when the genes that predispose to schizophrenia are expressed in the brain would be valuable, as it would suggest different avenues for investigation and might also suggest optimal times for therapeutic intervention.

The complexity of schizophrenia genetics is illustrated by a well-studied chromosomal translocation that was discovered in a large Scottish family. This translocation between chromosomes 1 and 11 inactivates a gene that came to be called Disrupted in Schizophrenia-1 (*Disc*-1) that appears to have significant roles in brain development. Within this multigenerational family, individuals who inherited the translocation exhibit serious mental illness but not necessarily schizophrenia. Some have bipolar disorder and others have major depression. Thus truncations in *Disc*-1 must interact with other genes and nongenetic factors to determine the ultimate phenotype.

Attempts to identify objectively measurable components of schizophrenia and other psychiatric disorders have focused on what have been called intermediate phenotypes or endophenotypes. Intermediate phenotypes may represent measurable structural brain abnormalities—cognitive abnormalities (such as deficits in working memory) measured by their neural correlates on functional neuroimaging—or they may represent measurable neurochemical abnormalities. If intermediate phenotypes can successfully be identified, they may simplify the search for risk genes because they may help identify more homogeneous populations for study than those identified by clinical symptoms and interviewing alone.

The search for modifiable environmental risk factors has also proved daunting because some environmental factors that correlate with the disease may be a result rather than a cause of schizophrenia and others may be proxies for the actual, but as yet undiscovered risks. For example, a consistent relationship has been found between schizophrenia and low socioeconomic status. However, the evidence suggests that schizophrenia itself impairs occupational and social success, leading to downward socioeconomic drift, rather than the alternative notion that stressors associated with poverty contribute to the disease. Other environmental risk factors, including season of birth, urban birth, maternal exposure to viral illness, paternal age, and perinatal complications, have been identified in population studies. Understanding the aspects of urban birth that might contribute to the risk of schizophrenia poses a significant challenge.

Neuroanatomic Abnormalities May Be a Causative Factor in Schizophrenia

Schizophrenia is characterized by certain abnormalities in brain anatomy that can be seen with structural and functional magnetic resonance imaging (fMRI). Thinning of specific areas of the prefrontal, temporal, and parietal cerebral cortex has been observed in many studies (Figure 62–2). The thinning of the prefrontal cortex is most pronounced in the dorsolateral prefrontal cortex, the brain region most critical for working memory.

Thinning in the temporal lobe has been traced to a loss of gray matter in the superior temporal gyrus, the temporal pole, the amygdala (amygdala reductions may be limited to males), and the hippocampus. These regions are normally involved in integrating cognition and emotion. The loss of gray matter is counterbalanced by an increase in the volume of the cerebral ventricles (Figure 62–3).

Structural abnormalities in the brain, such as loss of cortical gray matter, have been correlated with functional abnormalities both in cognitive performance tests and studies with positron emission therapy (PET) or fMRI. Impairment of functions that are dependent on the prefrontal cortex have been particularly well documented. For example, patients with schizophrenia have deficits in working memory and cognitive control, which are correlated in functional neuroimaging studies with lack of activity in the dorsolateral prefrontal cortex.

Loss of Gray Matter in the Cerebral Cortex Appears to Result from Loss of Synaptic Contacts Rather Than Loss of Cells

The observed loss of volume in the frontal and temporal cortical regions is not the result of cell death (loss of cell bodies) but rather a reduction in dendritic, axonal, and synaptic processes (neuropil). As a consequence, the density of cells in the cerebral cortex increases. More cells per unit volume and less total gray matter contribute to enlargement of the ventricular spaces.

Like the prefrontal and temporal cortex, the thalamus also appears smaller in patients with schizophrenia compared to nonaffected individuals. But cell counts in postmortem tissue suggest that, unlike the cerebral cortex, there may be loss of cell bodies in the mediodorsal nucleus of the thalamus. Because cells of

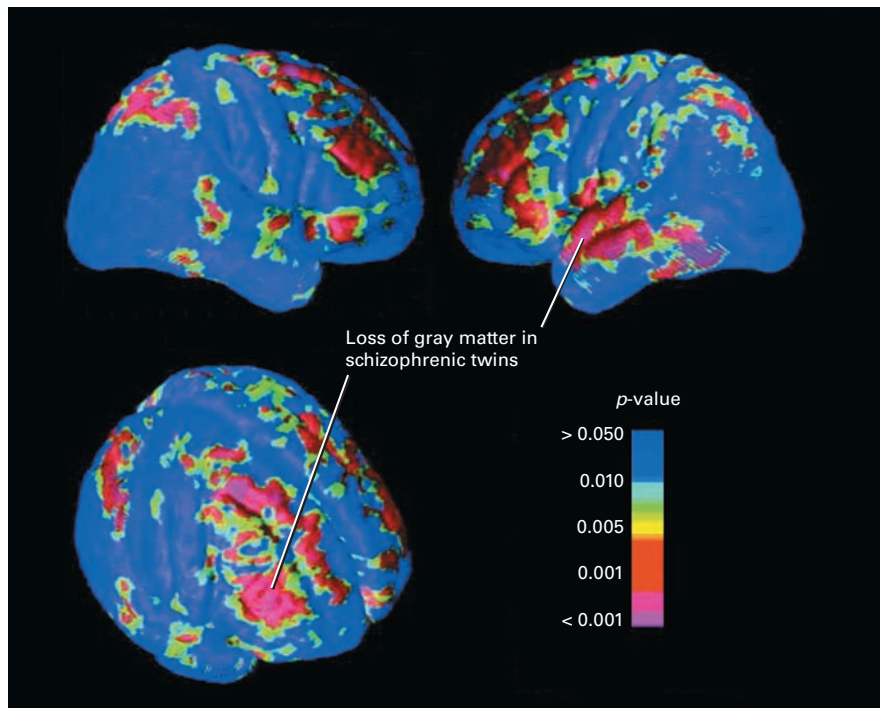
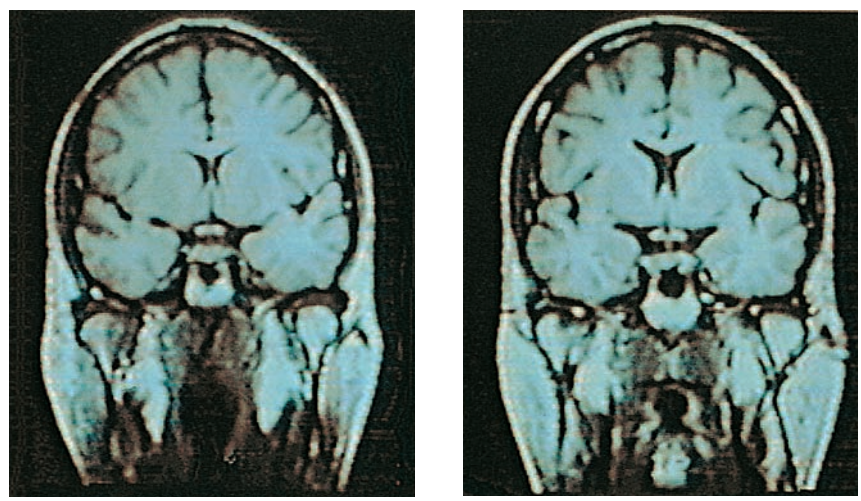


Figure 62–2 Gray matter loss in schizophrenia. Gray matter loss is well documented in schizophrenia; unaffected first-degree relatives also show some loss of cortical gray matter. A study of monozygotic and dizygotic twin pairs discordant for schizophrenia and healthy matched control twins showed that there are significant gray matter deficits in those at genetic risk for schizophrenia. However, among the affected members of twin pairs there are additional, disease-specific deficits in dorsolateral prefrontal, superior temporal, and superior parietal association areas. These reflect the influence of nongenetic factors (eg, developmental or environmental factors). The disease-specific gray matter loss correlates with symptom severity and degree of cognitive dysfunction rather than with duration of illness or drug treatment. The images here show regional deficits in gray matter in schizophrenic monozygotic twins relative to their healthy co-twins (n = 10 pairs) viewed from the right, left, and right-oblique perspectives. Differences in twins are illustrated by the pseudocolor scale superimposed on cortical surface maps, with pink and red indicating the greatest statistical significance. (Reproduced, with permission, from Cannon et al. 2002.)



Unaffected twin Schizophrenic twin

Figure 62–3 Enlargement of lateral ventricles in schizophrenia. This MRI compares monozygotic co-twins discordant for schizophrenia. The affected member of the twin pair has the characteristically enlarged ventricles of schizophrenia. Because there is a wide range of normal ventricular volumes in the population, an unaffected monozygotic twin serves as a particularly appropriate control subject. As with Figure 62–2, this comparison also illustrates the role of nongenetic factors in schizophrenia because monozygotic twins have identical genomes.

the mediodorsal nucleus send their axons to the dorsolateral prefrontal cortex, loss of these axonal terminals could in turn contribute to the reduction of cortical dendrites and the dendritic spines that usually receive these thalamocortical connections.

Pyramidal neurons, the most common type of excitatory neuron in the neocortex, receive excitatory input from the thalamus on dendritic spines. Thus the reduction in dendrites and dendritic spines (Figure 62–4) would likely signify a loss of synaptic contacts in the dorsolateral prefrontal cortex in schizophrenia. The loss of synaptic connections in this region could possibly explain the impairment of working memory and executive function that characterizes schizophrenia (Figure 62–5).

Abnormalities in Brain Development During Adolescence May Contribute to Schizophrenia

Because schizophrenia first occurs typically in late teenage years or in the early twenties, symptoms may be triggered by abnormalities in late stages of brain development. Early adulthood is an important period of brain development, as the brain matures in response to a variety of influences. These range from gonadal steroids in adolescence to stressful life experiences such as separating from parents and siblings for college or military service, or becoming independent by taking on adult responsibilities such as employment and sexual relationships.

During this period critical life events are accompanied by synaptic pruning that is part of the selective maintenance of those synaptic connections that are used effectively during normal brain development. Synaptic pruning may be particularly important in the prefrontal cortex. Moreover, the pruning coincides with major changes in dopaminergic neurotransmission in this brain area during late adolescence. The timing of these processes is consistent with the implication of both prefrontal cortex and the dopaminergic system in the pathogenesis of schizophrenia (Figure 62–5).

Although slow continued loss of gray matter in prefrontal and temporal cortex has been observed after diagnosis, cortical abnormalities and ventricular enlargement are generally observed at the time of first diagnosis, suggesting that the pathogenic processes underlying schizophrenia have been active long before psychotic symptoms emerge.

Figure 62–4 Decreased dendritic spine density in schizophrenia. Brightfield photomicrographs illustrate Golgi-impregnated basilar dendrites and spines of pyramidal neurons in layer III in the dorsolateral prefrontal cortex in a normal control subject and two subjects with schizophrenia. Note the loss of dendritic spines in the schizophrenic subjects. (Reproduced, with permission, from Glantz and Lewis 2000.)

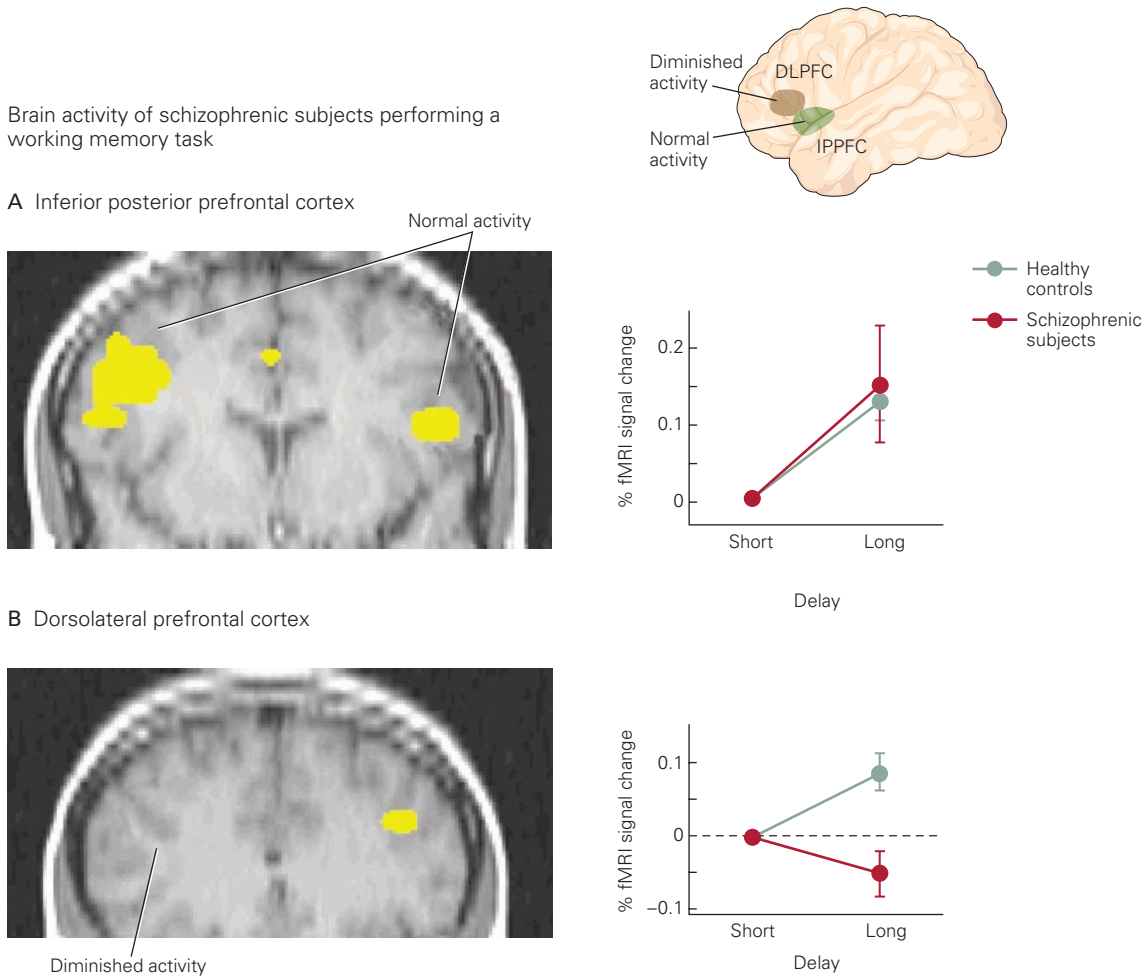


Figure 62–5 Deficits in the function of prefrontal cortex in schizophrenia. Functional MRI (fMRI) was used to examine activity in prefrontal cortex in patients with schizophrenia (first-episode patients who had never been given antipsychotic drugs) as well as healthy controls during performance of a working memory task. Subjects were presented with a sequence of letters and instructed to respond to a particular letter (the "probe" letter) only if it immediately followed another specified letter (the "contextual cue" letter). Demands on working memory were increased by increasing the delay between the cue and the probe letters. A longer delay places greater demands on working memory. The greater demand is hypothesized to require greater activation of prefrontal cortical circuits. (Reproduced, with permission, from Barch et al. 2001.)

A. In both schizophrenic patients and controls activation within Brodmann's area 44/46 increases normally with increases in demand on working memory, suggesting that these inferior posterior regions of prefrontal cortex (IPPFC) have intact function in schizophrenia. The plot shows the signal change that occurs in the "long-delay" and "short-delay" conditions in healthy controls and patients with schizophrenia based on the activity in the right side of the prefrontal cortex shown in the fMRI scan. Similar effects were observed for activity in the left-side.

B. There is less activity in Brodmann's area 46/49, a region of dorsolateral prefrontal cortex (DLPFC), in patients with schizophrenia relative to healthy controls. Unlike the areas of prefrontal cortex shown in part A, Brodmann's area 46/49 is not activated normally in subjects with schizophrenia. The plot shows that, unlike IPPFC, DLPFC in schizophrenic subjects fails to activate in the long-delay relative to the short-delay condition, consistent with the deficit in working memory function shown by patients with schizophrenia. Selective impairment of one region of prefrontal cortex alongside other regions that appear to have normal function suggests that the impairment is caused by a regionally specific process rather than a diffuse and nonspecific pathophysiological process.

Comparisons of middle-aged and older monozygotic twins that are discordant for schizophrenia (and in which the unaffected twin serves as a control) have shown that the severity of gray matter deficits in the prefrontal cortex correlate with severity of symptoms, not with the duration of illness. Of course, such studies cannot tell us whether the deficits were fully present at the onset of symptoms. To address this issue Judith Rapoport conducted a longitudinal study of those rare individuals with onset of schizophrenia in childhood and documented a correlation between progression of gray matter deficits and ventricular enlargement with time and duration of illness. In these subjects the normal loss of gray matter during adolescence, presumably related to normal processes of synaptic pruning, was exaggerated (Figure 62–6).

Antipsychotic Drugs Act on Dopaminergic Systems in the Brain

The antipsychotic drugs used to treat schizophrenia all act on the dopaminergic pathways of the forebrain. The first effective antipsychotic drug, chlorpromazine,

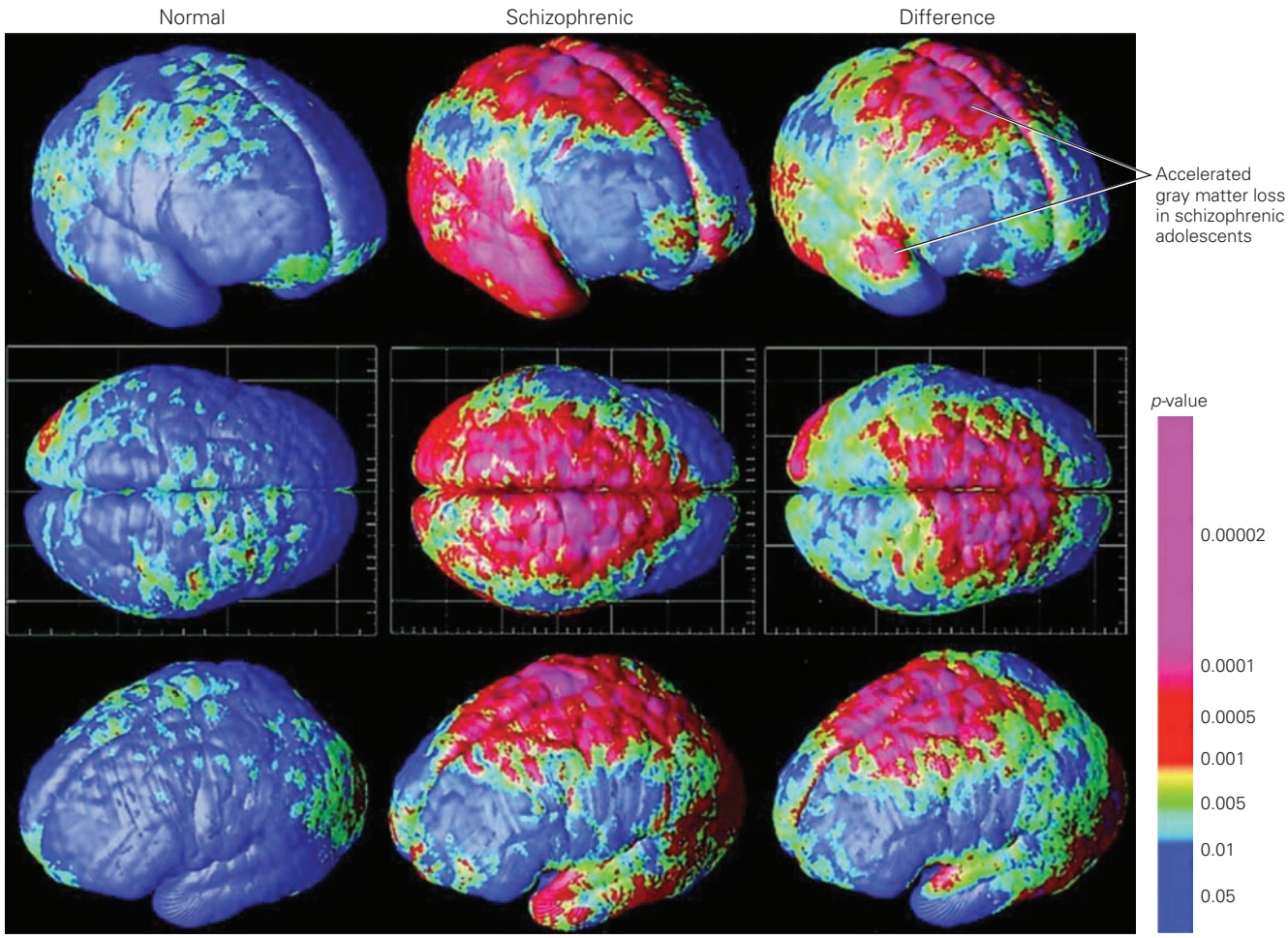


Figure 62–6 Normal loss of gray matter in adolescence is accelerated in adolescents with schizophrenia. The volume of gray matter in parietal, motor, supplementary motor, and superior frontal areas of cerebral cortex is progressively reduced during adolescence because of normal processes of synaptic pruning. In schizophrenic adolescents the loss of gray matter is more pronounced in broad regions of temporal cortex, including the superior temporal gyrus. The loss of gray matter attributable to schizophrenia (right column) can be determined by comparing the average rates of gray matter loss in normal and schizophrenic adolescents. Significant differences are shown in the pseudocolor scale superimposed on the cortical maps. (Reproduced, with permission, from Thompson et al. 2001.)

was developed for its antihistaminic and sedating effects and not for its psychiatric effects. Chlorpromazine was later found to be effective in treating the agitation of patients with schizophrenia and manic depressive illness. Based on these acute calming effects, chlorpromazine and many related drugs were initially described as major tranquilizers. By the mid 1960s, however, it became clear that these drugs were not simply acting as tranquilizers but were specifically reducing the positive symptoms of schizophrenia, such as hallucinations and delusions. They were also effective in treating the psychotic symptoms that can occur in mood disorders, such as mania or severe depression.

The antipsychotic drugs had less impact on the negative symptoms of schizophrenia and little or no impact on cognitive deficits. Patients did improve enough to leave the hospital. Indeed, the widespread use of antipsychotic drugs paved the way for the large-scale release of patients with schizophrenia from psychiatric institutions. Unfortunately, these patients did not return to their premorbid level of functioning. The recognition that the sedating properties of early antipsychotic drugs were undesirable side effects led to the development of newer less sedating antipsychotic compounds. In addition, all of the first-generation antipsychotic drugs, with the exception of clozapine, produced Parkinson-like side effects in the extrapyramidal tract such as stiffness, tremor, and difficulty initiating movements.

Because Parkinson disease is caused by the loss of dopaminergic neurons in the midbrain, the occurrence of Parkinson-like symptoms with antipsychotic drug treatment suggested to Arvid Carlsson that these drugs decreased dopaminergic transmission. Following up on this idea, Carlsson established that the antipsychotic drugs block dopamine receptors. Two families of dopamine receptors are known. The D_1 family, which in humans includes D_1 and D_5, are coupled to stimulatory G proteins that activate adenylyl cyclase. The D_2 family, which includes D_2, D_3, and D_4, are coupled to the inhibitory G protein (G_i) that inhibits the cyclase. The D_2 family of receptors has also been shown to signal through an independent pathway involving β arrestin$_2$ (β-arr$_2$) and Akt, a protein kinase previously known as protein kinase B. The family of D_1 receptors are expressed in the striatum and are the major type of dopamine receptor in the cerebral cortex and hippocampus, while the D_2 family of receptors is expressed most densely in the striatum, but also in the cerebral cortex, amygdala, and hippocampus. Correlations between receptor binding studies and clinical efficacy in reducing positive psychotic symptoms indicate that the D_2 family is the main target of the therapeutic actions of antipsychotic drugs on positive symptoms (Figure 62–7).

Antipsychotic drugs not only treat acute relapses of schizophrenia and other psychotic disorders, but continuous treatment with these drugs reduces hospitalization because it markedly increases the time between relapses. Unfortunately, the side effects that occur with administration limit their long-term use. A second generation of antipsychotic medications has been developed based on the observation that clozapine has less likelihood of causing Parkinsonian side effects than the other drugs and can also produce

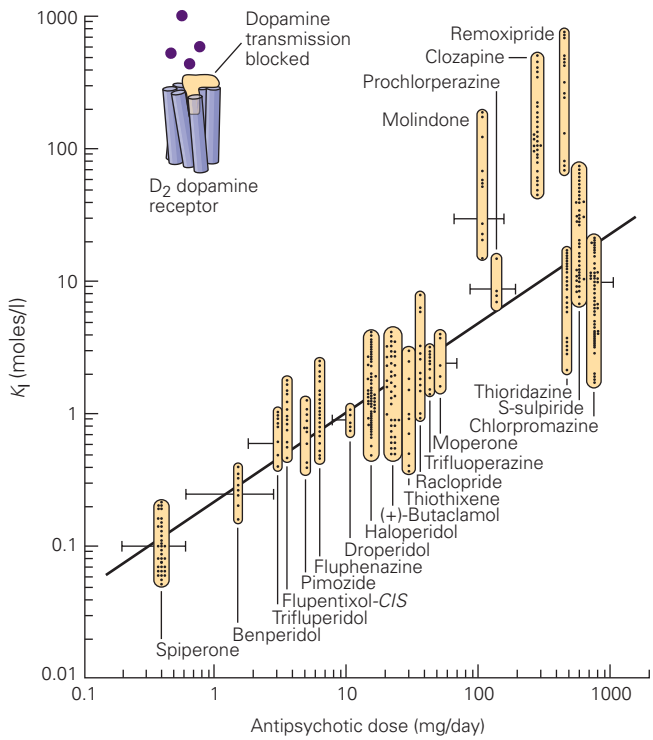


Figure 62–7 The potency of first-generation antipsychotic drugs in treating positive symptoms is strongly correlated with their affinity for D_2 dopamine receptors. On the horizontal axis is the average daily dose required to achieve similar levels of clinical efficacy. On the vertical axis is K_i, concentration of drug required to bind 50% of D_2 receptors in vitro. The higher the drug concentration required, the lower the affinity of the drug for the receptor. The measurements on the two axes are not entirely independent of each other as the ability of a drug to block dopamine D_2 receptors in vitro is often used to help determine doses to be tested in clinical trials. Clozapine, which does not fall on the line, has significantly greater efficacy than the others, although its mechanism of action is not well understood. (Adapted, with permission, from Seeman et al. 1976.)

therapeutic responses in some patients with schizophrenia for whom other drugs have not worked. (Unfortunately clozapine has other serious side effects that limit its use.)

Based on the properties of clozapine, some of the second-generation drugs were designed to have somewhat lower affinity for D_2 receptors than the first-generation drugs, and some also block the serotonin 5-HT_{2A} receptors, an action that was thought to protect against motor side effects. Recent large-scale clinical trials of the newer drugs have been disappointing, however, showing little incremental benefit over the older antipsychotic drugs. None of the newer drugs is equal to clozapine in efficacy.

Because drugs that reduce positive symptoms do so by blocking D_2 receptors, investigators have asked: What is the role of dopamine in the symptoms of schizophrenia? Although some drugs that block D_2 receptors reduce psychotic symptoms, other drugs that increase dopamine at synapses (such as amphetamine and cocaine) can produce psychotic symptoms, especially paranoid symptoms. Thus Carlsson suggested that dopaminergic systems are hyperactive in schizophrenia.

The most direct evidence for this idea comes from studies in the mid-1990s that found that amphetamine-produced increases in dopamine release were greater in schizophrenic patients than in healthy subjects. These studies suggest that abnormalities in amphetamine-sensitive processes—such as dopamine storage, vesicular transport, dopamine release, or dopamine reuptake by presynaptic neurons—might lead to hyperactivity in the subcortical dopaminergic systems and could contribute to the positive symptoms of schizophrenia, the symptoms that respond to antipsychotic drugs.

Although dopamine activity might increase in subcortical regions of the brain in schizophrenia, there is also some evidence that it might decrease in cortical regions and that this might contribute to the cognitive symptoms. In particular, the number of D_1 dopamine receptors in the prefrontal cortex is thought to be reduced in schizophrenia, an interesting idea because D_1 receptors have been shown to play a role in working memory and executive functions reliant on prefrontal cortex.

Glutamate, the major excitatory neurotransmitter in the brain, also has been implicated in schizophrenia, albeit indirectly. Phencyclidine and ketamine, which block the NMDA-type glutamate receptor and which were originally developed as anesthetic agents, produce psychotic symptoms. In healthy subjects ketamine also produces cognitive dysfunction that mimics, at least to a degree, the cognitive abnormalities seen in schizophrenia. This has led several investigators to explore the idea that decreased function of NMDA-type glutamate receptors might play a role in producing some of the positive and cognitive symptoms of schizophrenia. These studies indicate that positive and cognitive symptoms are probably the result of abnormalities in several transmitter systems that act either in parallel or in combination with dopamine.

An Overall View

Schizophrenia is a chronic, profoundly disabling disorder characterized by dramatic psychotic symptoms, as well as deficits in emotion, motivation, and cognition. The cognitive deficits impair the ability of people with schizophrenia to regulate their behavior in accordance with reasonable, stable goals. The result is that people with schizophrenia are frequently unable to hold down simple jobs, even at those times when antipsychotic drugs effectively control their hallucinations and delusions.

Once considered a purely psychological reaction to the family environment, it is now clear that schizophrenia is highly influenced by genetic risk factors; indeed, with modern genetic technologies the first convincing risk genes are being identified.

Postmortem studies and neuroimaging are documenting loss of gray matter in the prefrontal and temporal cerebral cortex. Functional neuroimaging is revealing the basis of the disabling cognitive symptoms. Despite this progress, the drugs that we have to treat schizophrenia, as useful as they are, still leave patients seriously symptomatic awaiting new discoveries from neural science.

Steven E. Hyman
Jonathan D. Cohen

Selected Readings

Cohen JD, Servan-Schreiber D. 1992. Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. Psychol Rev 99:45–77.

Harrison PJ. 1999. The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain 122:593–624.

Kerns JG, Berenbaum H. 2002. Cognitive impairments associated with formal thought disorder in people with schizophrenia. J Abnorm Psychol 111:211–224.

Lewis DA, Levitt P. 2002. Schizophrenia as a disorder of neurodevelopment. Annu Rev Neurosci 25:409–432.

Nestler EJ, Hyman SE, Malenka RJ. 2001. *Molecular Neuropharmacology. A Foundation for Clinical Neuroscience*. New York: McGraw-Hill.

References

Arnold SE, Trojanowski JQ, Gur RE, Blackwell P, Han LY, Choi C. 1998. Absence of neurodegeneration and neural injury in the cerebral cortex in a sample of elderly patients with schizophrenia. Arch Gen Psychiatry 55:225–232.

Barch DM, Carter CS, Braver TS, Sabb FW, MacDonald AW, Noll DC, Cohen JD. 2001. Selective deficits in prefrontal cortex function in medication-naïve patients with schizophrenia. Arch Gen Psychiatry 58:280–288.

Barch DM, Berenbaum H. 1996. Language production and thought disorder in schizophrenia. J Abnormal Psychiatry 105:81–88.

Beaulieu JM, Gainetdinov RR, Caron MG. 2009. Akt/GSK3 signaling in the action of psychotropic drugs. Annu Rev Pharmacol Toxicol 49:327–47.

Cannon TD, Thompson PM, van Erp TG, Toga AW. 2002. Cortex mapping reveals regionally specific patterns of genetic and disease-specific gray-matter deficits in twins discordant for schizophrenia. Proc Natl Acad Sci U S A 99:3228–3233.

Carter CS, Mintun M, Nichols T, Cohen JD. 1997. Anterior cingulate gyrus dysfunction and selective attentional dysfunction in schizophrenia: an 150-H20 PET study during Stroop task performance. Am J Psychiatry 154:1670–1675.

Chapman LJ, Chapman JP, Miller GA. 1964. A theory of verbal behavior in schizophrenia. In: BA Maher (ed). *Progress in Experimental Personality Research*. New York: Academic Press.

Geyer MA, Swerdlow NR, Mansbach RS, Braff DL. 1990. Startle response models of sensorimotor gating and habituation deficits in schizophrenia. Brain Res Bull 25: 485–498.

Glahn DC, Therman S, Manninen M, Huttunen M, Kaprio J, Lonnqvist J, Cannon TD. 2003. Spatial working memory as an endophenotype of schizophrenia. Biol Psychiatry 53:624–626.

Glantz LA, Lewis DA. 2000. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Arch Gen Psychiatry 57:65–73.

Gottesman II. 1991. *Schizophrenia Genesis: The Origins of Madness.* New York: Freeman.

Green MF. 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 153:321–330.

Heaton RK, Gladsjo JA, Palmer BW, Kuck, J, Marcotte, TD, Jeste DV. 2001. Stability and course of neuropsychological deficits in schizophrenia. Arch Gen Psychiatry 58:24–32.

Kane J, Honigfeld G, Singer J, Meltzer H. 1988. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 45:789–796.

Kety SS, Rosenthal D, Wender PH, Schulsinger F. 1968. The types and prevalence of mental illness in the biological and adoptive families of adopted schizophrenics. J Psychiatry Res 6:345–362.

Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, Erdos J, McCance E. 1996. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. Proc Natl Acad Sci U S A 93:9235–9240.

Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck PA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsaio JK. 2005. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 353:1209–1223.

McGrath J, Saha S, Chant D, Welham J. 2008. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 30:67–76.

Millar JK, Wilson-Annan JC, Anderson S, Christie S, Taylor MS, Semple CA, Devon RS, et al. 2000. Disruption of two novel genes by a translocation co-segregating with schizophrenia. Hum Mol Genet 22:1415–1423.

Mortensen PB, Pedersen CB, Westergaard T, Wohlfahrt J, Ewald H, Mors O, Andersen PK, Melbye M. 1999. Effects of family history and place and season of birth on the risk of schizophrenia. N Engl J Med 340:603–608.

Owen MJ, Craddock N, O'Donovan MC. 2010. Suggestion of roles for both common and rare risk variants in genome-wide studies of schizophrenia. Arch Gen Psychiatry 67:667–673.

Popken GJ, Bunney WE Jr, Potkin SG, Jones EG. 2000. Subnucleus-specific loss of neurons in medial thalamus of schizophrenics. Proc Natl Acad Sci U S A 97:9276–9280.

Rajkowska G, Selemon LD, Goldman-Rakic PS. 1998. Neuronal and glial somal size in the prefrontal cortex: a postmortem morphometric study of schizophrenia and Huntington disease. Arch Gen Psychiatry 55:215–224.

Rapoport JL, Giedd JN, Blumenthal J, Hamburger S, Jeffries N, Fernandez T, Nicolxon R, Bedwell J, Lenane M, Zijdenbos A 1999. Progressive cortical change during adolescence in childhood-onset schizophrenia. A longitudinal magnetic resonance imaging study. Arch Gen Psychiatry 56:649–654.

Ripke S, Sanders AR, Kendler KS, Levinson DF, Sklar P, Holmans PA, Lin D-Y. 2011. Genome-wide association study identifies five new schizophrenia loci. Nat Genet 43: 969–976.

Seeman P, Lee T, Chau-Wong M, Wong K. 1976. Antipsychotic drug doses and neuroleptic/dopamine receptors. Nature 261:717–719.

Silver H, Feldman P, Biolker W, Gur RC. 2003. Working memory deficit as a core neuropsychological dysfunction in schizophrenia. Am J Psychiatry 160:1809–1816.

Suddath RL, Christison GW, Torrey EF, Casanova MF, Weinberger DR. 1990. Anatomical abnormalities in the

brains of monozygotic twins discordant for schizophrenia. N Engl J Med 322:789–794.

Thompson PM, Vidal C, Giedd JN, Gochman P, Blumenthal J, Nicolson R, Toga, AW, Rapoport J. 2001. Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. Proc Natl Acad Sci U S A 98:11650–11655.

van Haren NE, Schnack HG, Cahn W, van den Heuvel MP, Lepage C, Collins L, Evans AC, Hulshoff Pol HE, Kahn RS. 2011 Changes in cortical thickness during the course of illness in schizophrenia. Arch Gen Psychiatry 68: 871–880.

Walsh T, McClellan JM, McCarthy SE, Addington AM, Pierce SB, Cooper GM, Nord AS, et al. 2008. Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. Science 320:539–543.