nucleotide polymorphism that confers a small increment in risk (typically 5%–10%) for schizophrenia. The value of such allelic variants is as a tool to identify genes that play a role in the molecular mechanism of disease. In turn, the implicated genes help identify molecular pathways that can potentially be exploited in the development of therapeutic drugs.

In addition to the utility of genetics for discovering biological processes involved in disease, it can also contribute to the stratification of study populations in epidemiological and clinical studies. A person's risk of schizophrenia or other disorders can be estimated by calculating his or her total burden of common risk alleles for the condition. The result is a polygenic risk score, a measure that is increasingly being used to stratify populations by genetic susceptibility to schizophrenia in both clinical studies and in epidemiologic studies of environmental risk factors.

Environmental risk factors for schizophrenia that have been replicated across studies include nutrient deprivation in utero (notably in studies following famines), season of birth (winter and early spring birth), urban birth, and migration. The analysis of causal factors within such broad categories of exposure is likely to benefit from knowing who is susceptible. Moreover, clues to environmentally induced causal pathways may be found in the risk genotypes of those with schizophrenia who have had a particular exposure.

Given the lack of objective diagnostic tests, current diagnostic criteria, such as those within the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, are based on clinical observation and course of illness. As a result, individuals currently diagnosed with schizophrenia are highly heterogeneous. Polygenic risk scores can explain only a portion of the variance in schizophrenia cohorts, and the scores provide only probabilistic information. However, they represent the first objective tool that permits stratification of subjects diagnosed with schizophrenia. As such, the application of such scores may begin to diminish heterogeneity in clinical studies ranging from neuroimaging to neurophysiological studies to treatment trials.

Although almost all cases of schizophrenia reflect polygenic risks, as predicted by Gottesman, a small percentage of cases are highly influenced by the presence of a penetrant mutation that typically exerts pleiotropic effects, including intellectual disability, resulting in what is often called syndromic schizophrenia. Most of these penetrant mutations are copy number variants: deletions, duplications, or sometimes triplications of a particular segment of a chromosome.

The most common and best studied cause of syndromic schizophrenia is the 22q11.2 microdeletion, which accounts for approximately 1% of patients diagnosed with schizophrenia. The microdeletion typically occurs de novo and results in loss of one of two copies of 38 to 44 genes. As is typical for such copy number variations, those affected suffer from a complex of symptoms. The syndrome accompanying the 22q11.2 microdeletion, sometimes called velocardiofacial or DiGeorge syndrome, includes cognitive disability, cardiovascular defects, and facial dysmorphology. The penetrance of each of these symptoms and signs is independent of the others; thus, affected individuals have different combinations of phenotypes. Individuals with the 22q.11.2 microdeletion have a 25% to 40% risk of schizophrenia and a 20% risk of autism. Other syndromic forms of psychosis are similarly variable.

Syndromic forms of schizophrenia can provide important windows into the biology of psychosis, even if their similarities to common polygenic types of schizophrenia are still a matter of study. One powerful advantage of penetrant mutations is the ability to generate cellular and animal models in order to characterize their effects on brain structure and function. A second advantage is the ability to prospectively study individuals carrying these mutations. Studying syndromic schizophrenia, therefore, has the potential to reveal much about basic pathophysiological mechanisms. One important area of investigation is how copy number variations and other high-penetrance mutations that lead to psychosis manifest based on a person's genetic background, specifically the many common DNA variants that influence risk. To this point, recent findings suggest that the propensity in individuals carrying a copy number variation to develop psychotic symptoms may result from a strong interaction of the copy number variation with the person's polygenic background risk for schizophrenia, suggesting significant shared mechanisms between schizophrenia associated with single genetic mutations and that associated only with polygenic variants.

Schizophrenia Is Characterized by Abnormalities in Brain Structure and Function

Abnormalities in the structure and function of the brain have been identified in schizophrenia both by postmortem examination and by a variety of noninvasive technologies in living patients. The best replicated finding, both by postmortem study and by structural MRI, is loss of gray matter in prefrontal, temporal, and parietal regions of cerebral cortex (Figure 60–2) with counterbalancing increases in the size of the cerebral ventricles (Figure 60–3). Thinning of the cerebral cortex

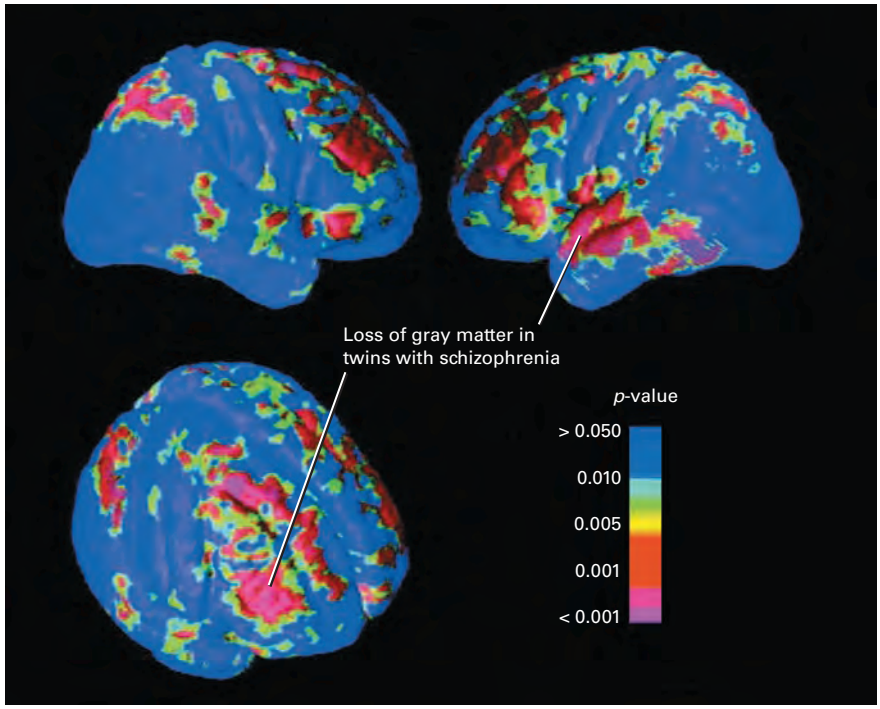

Figure 60–2 Gray matter loss in schizophrenia. Gray matter loss is well documented in schizophrenia. First-degree relatives who do not have a diagnosis of schizophrenia still often exhibit cortical gray matter loss intermediate between healthy individuals and those diagnosed with schizophrenia. Consistent with this, a study that examined losses of cortical gray matter in monozygotic and dizygotic twin pairs discordant for schizophrenia compared to healthy matched control twins found significant losses in those at genetic risk for schizophrenia but without the disease. Those members of twin pairs diagnosed with schizophrenia demonstrated additional, disease-specific cortical thinning in dorsolateral prefrontal, superior temporal, and superior parietal association areas. These additional defects appear to reflect the influence of nongenetic factors involved in pathogenesis (eg, developmental or environmental factors). The disease-specific gray matter loss correlates with the degree of cognitive impairment rather than with duration of illness or drug treatment. The images here show regional deficits in gray matter in monozygotic twins with schizophrenia 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.)

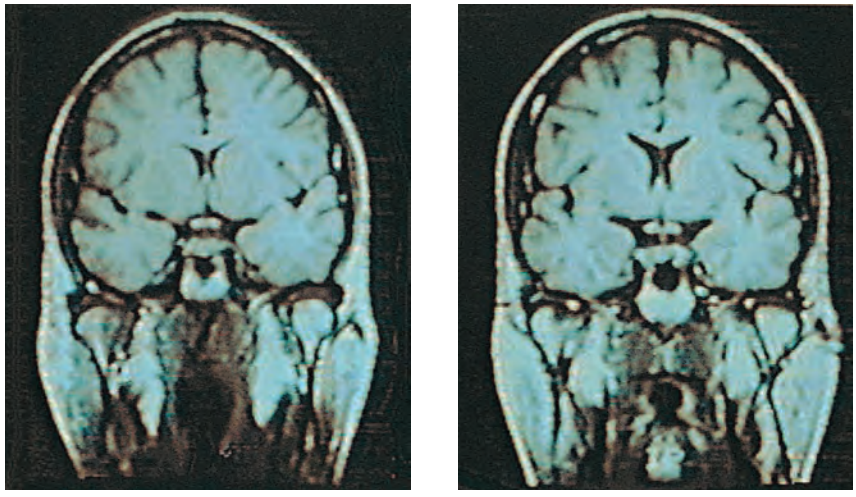

Figure 60–3 Enlargement of lateral ventricles in schizophrenia. Magnetic resonance imaging comparison of monozygotic twins discordant for schizophrenia. The affected member of the twin pair has the enlarged ventricles characteristic of schizophrenia. Because there is a wide range of normal ventricular volumes in the population, an unaffected monozygotic twin serves as a particularly appropriate control subject. Because monozygotic twins have identical genomes, this comparison also illustrates the role of nongenetic factors in schizophrenia.

is most pronounced in the dorsolateral prefrontal cortex, a brain region critical for working memory and thus cognitive control of thought, emotion, and behavior.

Loss of gray matter in the superior temporal gyrus, temporal pole, amygdala, and hippocampus in schizophrenia has also been correlated with impairments in cognition, recognition of emotions in others, and regulation of emotion in the affected person. Functional neuroimaging using positron emission tomography and functional MRI (fMRI) has demonstrated that patients' deficits in performing working memory tasks while being imaged are associated with decrements in the activation of dorsolateral prefrontal cortex, a brain region known to play a critical role in working memory (Figure 60–4).

There is also growing recognition that schizophrenia is characterized by disruptions in connectivity between brain regions (Figure 60–5). Anatomical connectivity can be measured by diffusion tensor imaging, which identifies major axon tracts as they course between brain regions. Functional connectivity between brain regions can be estimated physiologically by measuring the degree to which activity patterns in different brain regions correlate with each other, using such approaches as resting state fMRI and electrophysiology. Both imaging and physiological methods reveal that individuals with schizophrenia have deficits in the connections between brain regions. Weaker connections would likely impair cognition and complex behaviors.

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

Postmortem studies have examined the cellular abnormalities that underlie the gross anatomical findings and functional deficits in schizophrenia. These studies have revealed that gray matter loss in the prefrontal and temporal cortical regions is not the result of cell death but rather a reduction in dendritic processes. As a consequence, the packing 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.

A reduction in dendrites and dendritic spines on pyramidal neurons, the most common type of excitatory neuron in the neocortex (Figure 60–6), would likely signify a loss of synaptic contacts in affected brain regions in individuals with schizophrenia. The loss of synaptic connections could underlie abnormalities in long-range functional connectivity and failures to recruit prefrontal cortical regions during tasks that require working memory (Figures 60–4 and 60–5).

Abnormalities in Brain Development During Adolescence May Be Responsible for Schizophrenia

Schizophrenia exhibits a stereotypic onset between late adolescence and early adulthood, with cognitive decline and negative symptoms occurring months or years before the onset of psychosis. This timing suggests the pathogenesis of schizophrenia might involve abnormalities in the late stages of brain development during adolescence, when cognitive function, emotion regulation, and executive function normally mature.

Throughout development, neurons elaborate an excessively large number of synaptic connections. Generally, synapses are strengthened and preserved when they are utilized, while weak or inefficient synapses are eliminated through a process called pruning. The process of synaptic refinement, which involves both synaptogenesis and pruning, results in neural computations that are efficient and adapted to the environment. Experience-dependent synaptic refinement was first described in the visual cortex, where pruning of weak connections is necessary for the emergence of binocular vision (see Chapter 49). Synaptogenesis and pruning continue throughout life, making possible new learning and updating of older memories. However, superimposed on such local events are significant waves of synaptic pruning that are spatially specific and developmentally timed. The last such wave in human brain maturation occurs during adolescence and early adulthood, with pruning in the temporal and prefrontal association cortex. This late wave of pruning is followed by myelination of many axons in these areas of cortex.

In the early 1980s, Irwin Feinberg hypothesized that schizophrenia might result from abnormal and excessive synaptic pruning during adolescence. Postmortem examination of the brains of persons with schizophrenia subsequently demonstrated a reduction of dendritic spines, and of synapses, in prefrontal and temporal cortices. Studies in nonhuman primates, taken together with human postmortem and neuroimaging studies, suggest that loss of dendritic arbors does not result from antipsychotic medications taken by many individuals with schizophrenia. The onset of cognitive impairment and negative symptoms during this period is consistent with the idea that synaptic pruning somehow goes haywire, damaging the ability of the cerebral cortex to process information. When the overpruning hypothesis was first enunciated in the

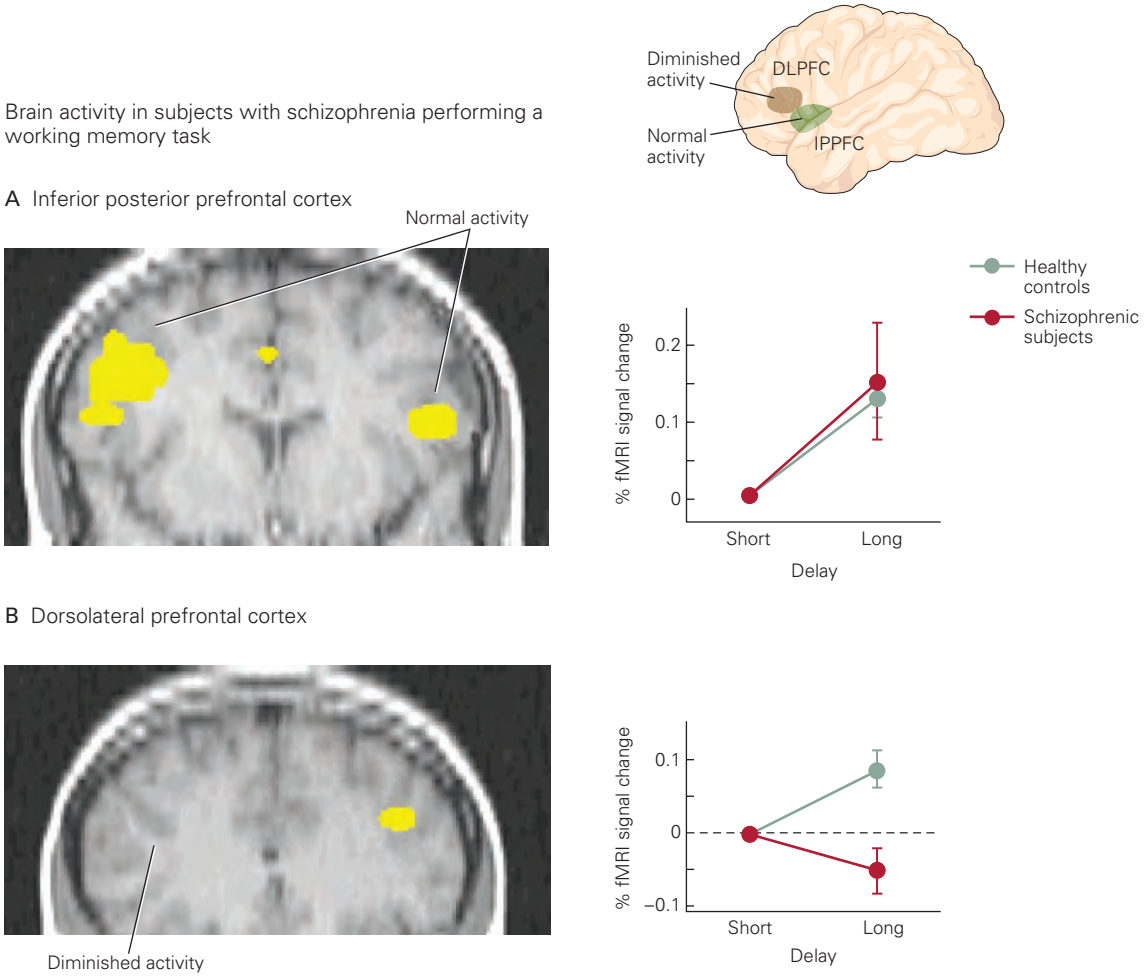

Figure 60–4 Deficits in the function of prefrontal cortex in schizophrenia. Functional magnetic resonance imaging (**fMRI**) was used to test the hypothesis that in patients with schizophrenia working memory engages circuits in the prefrontal cortex differently than in controls. Activity in the prefrontal cortex of two groups—patients with schizophrenia (first-episode patients who had never been given antipsychotic drugs) and healthy controls—was examined while subjects performed 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. The greater demand on working memory requires greater activation of prefrontal cortical circuits. (Adapted, with permission, from Barch et al. 2001.)

A. In both patients with schizophrenia and controls, normal increases in activation within inferior posterior regions of prefrontal cortex (**IPPFC**; Brodmann's area 44/46) as a function of demand on working memory suggest that the function of these regions remains intact in schizophrenia. The plot shows the fMRI signal change that occurs in the right side of the prefrontal cortex in the long-delay and short-delay conditions in healthy controls and in patients with schizophrenia. Similar effects were observed for 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 Brodmann's area 44/49 (shown in part **A**), Brodmann's area 46/49 is not activated normally in subjects with schizophrenia, consistent with the deficit in working memory seen in 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 due to a regionally specific process rather than a diffuse and nonspecific pathological process.

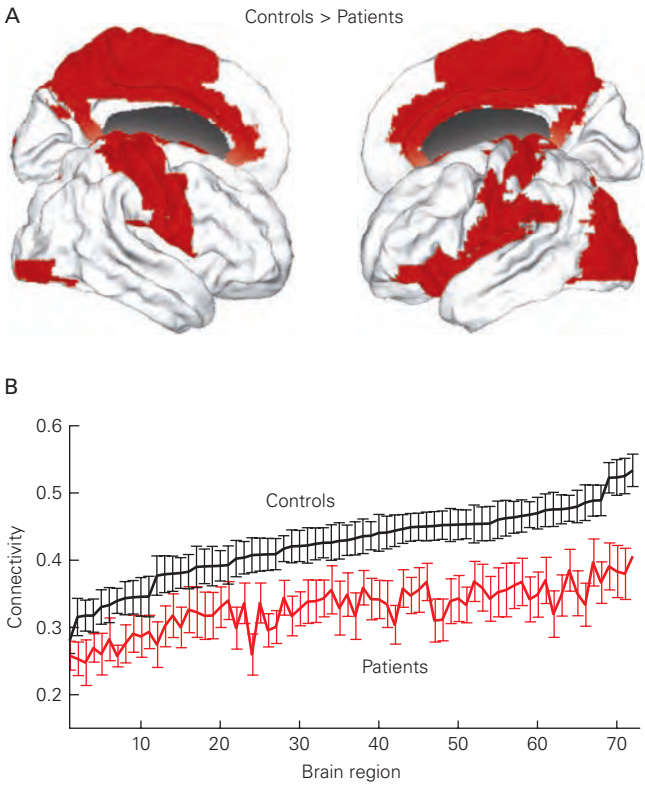

Figure 60–5 Decreased functional connectivity in schizophrenia. Correlations in neural activity between 72 defined brain regions were measured in patients with schizophrenia and in control subjects by resting state functional magnetic resonance imaging. (Reproduced, with permission, from Lynall et al. 2010.)

A. Brain regions that showed statistically significant reductions in functional connectivity in patients compared to controls are highlighted in **red**.

B. Mean (+/– standard error of the mean) functional connectivity between each brain region and the rest of the brain for patients and healthy controls.

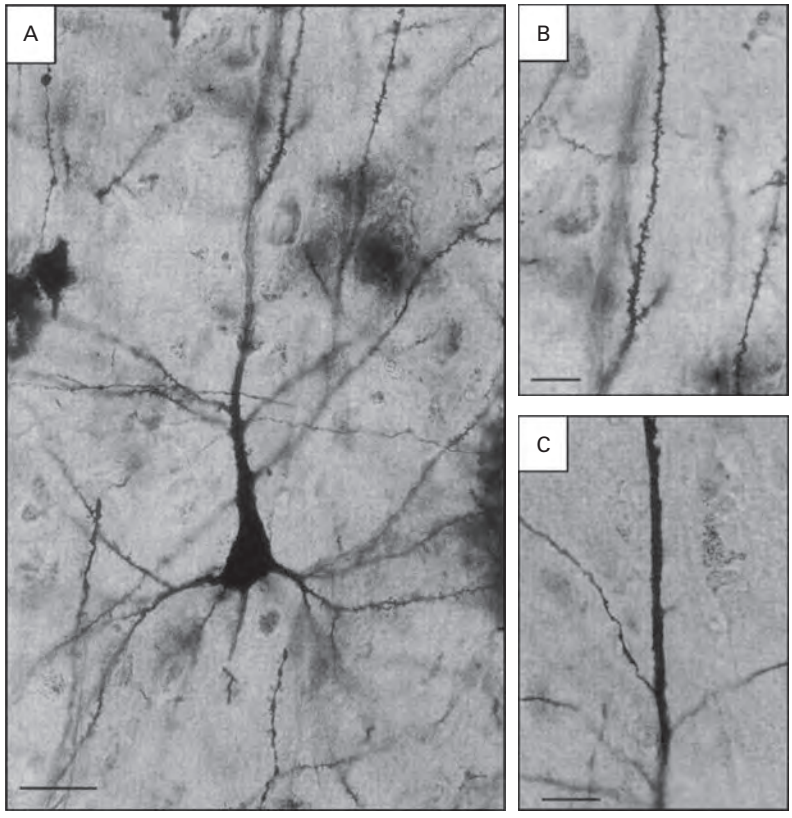

Figure 60–6 Photomicrographs of pyramidal neurons from the cerebral cortex from human brains stained by the Golgi method.

A. A layer III pyramidal neuron from a control brain, showing its morphology and its dendrites which are studded with spines.

B. A higher power view showing spines on a dendrite of a pyramidal neuron from a control brain.

C. A segment of a dendrite devoid of spines from the cerebral cortex of a person who had schizophrenia. (Scale: **A:** 30 µm; **B:** 20 µm; **C:** 15 µm.) Spine numbers are a rough proxy for the number of synaptic contacts onto the dendrite from other neurons; thus the paucity of spines in schizophrenia is consistent with fewer synaptic contacts than are found in the cerebral cortex of healthy brains.

(Reproduced, with permission, Garey et al. 1998. With permission from BMJ Publishing Group Ltd.)

1980s, it lacked a plausible molecular or cellular mechanism that might explain how synaptic pruning might go awry in schizophrenia. Recent genetic analysis may have provided a solution.

Unbiased, large-scale genetic studies have found that the strongest association with risk for schizophrenia lies within the major histocompatibility (MHC) locus on chromosome 6. The MHC locus encodes many proteins involved in immune function. Fine mapping of the locus pinpointed the largest genetic association signal to the genes encoding complement factor C4, a component of the classic complement cascade that, outside the brain, is involved in tagging microbes and damaged cells for engulfment and destruction by phagocytic cells. Subsequent analysis showed that the risk for schizophrenia is elevated as a function of increased expression in the brain of C4A (one of two isoforms). This finding adds support to the overpruning hypothesis because one function of the complement system in brain is to tag weak or inefficient synapses for removal by microglia (Figure 60–7).

Elevated expression of the complement factor C4A involved in synaptic pruning is certainly not the only mechanism leading to schizophrenia. As with any polygenic disorder, no one gene is necessary or sufficient for the disease phenotype. Thus, not everyone with schizophrenia has a high-risk C4A genotype, and not everyone with a high-risk C4A genotype develops schizophrenia. Many other genes are implicated in the risk for schizophrenia. Several such risk factors other than C4 are involved in regulation of the complement cascade, but the vast majority are not. Many of the genes associated with schizophrenia that have been identified to date are involved in various aspects of the structure and function of synapses; several encode ion channels. Thus, it seems likely that the genetic risk for schizophrenia involves, at least in part, synaptic function, synaptic plasticity, and synaptic pruning, and overpruning of synapses during adolescence is one plausible mechanism that should be explored further in studies of youth at high risk for schizophrenia. Nevertheless, other pathways, as yet less well characterized, may also turn out to be important. We have a long way to go in understanding the pathogenesis of schizophrenia.

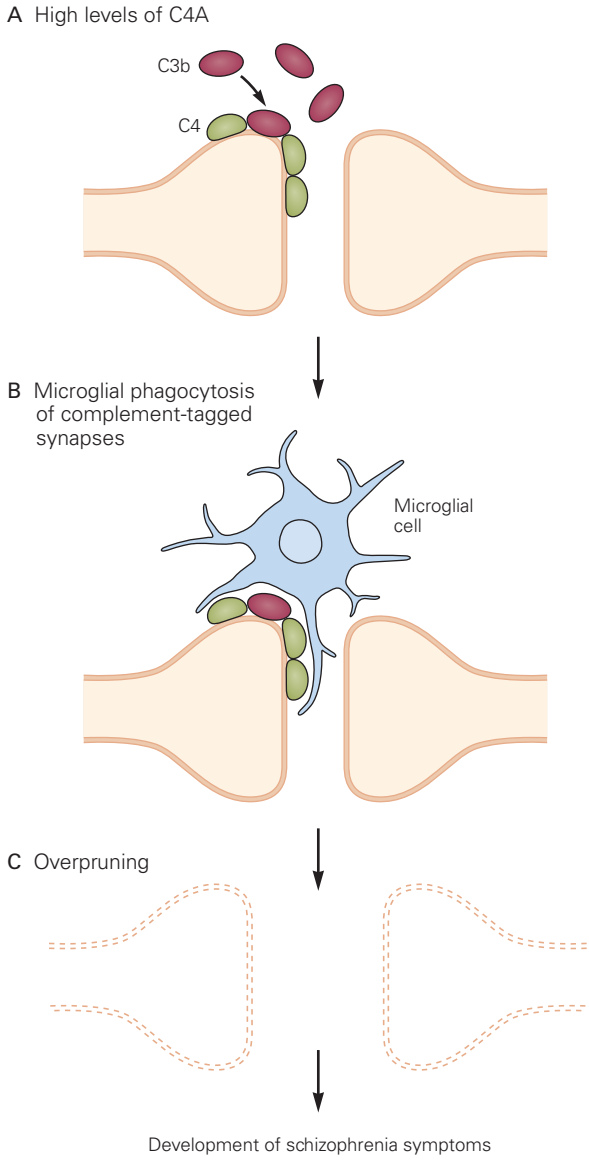

Figure 60–7 Complement factors and microglia have a role in synapse elimination. Maturation and plasticity of the nervous system involve both synaptogenesis and elimination of weak synapses. Complement factor 3b (**C3b**) is thought to serve as a "punishment signal" that identifies weak synapses for phagocytosis by microglia. Complement factor 4 (**C4**), a component of the complement cascade, is synthesized by neurons and astrocytes and recruits C3b to weak synapses. In humans, a complex genomic locus on chromosome 6 contains varying numbers of copies of the genes that encode the complement factor C4 proteins, C4A and C4B. Variants within this locus that give rise to high levels of C4A expression in brain increase schizophrenia risk. (Reproduced, with permission, from Christina Usher and Beth Stevens.)

Antipsychotic Drugs Act on Dopaminergic Systems in the Brain

All current antipsychotic drugs produce their therapeutic effects by blocking D_2 dopamine receptors in the forebrain. These drugs have many other effects at

various neurotransmitter receptors and intracellular signaling pathways, but these other actions primarily influence their side effects, not their main therapeutic mechanisms (Figure 60–8).

The first effective antipsychotic drug, chlorpromazine, was developed for its antihistaminic and sedating effects and was first investigated as a surgical preanesthetic by Henry Laborit in 1952. Based on its sedating effects, it was tested in psychotic patients soon thereafter. These tests showed, surprisingly, reduced hallucinations and delusions; indeed, the sedative effect of chlorpromazine is now considered a side effect. The success of chlorpromazine led to attempts to discover other antipsychotic drugs. Although many chemically diverse antipsychotic drugs are now in use, all share the same initial action of chlorpromazine in the brain, the ability to block the D_2 dopamine receptor. As a class, these drugs ameliorate psychotic symptoms not only in schizophrenia, but also in bipolar disorder, severe depression, and various neurodegenerative disorders. None of the antipsychotic drugs provide effective treatment for the cognitive impairments or deficit symptoms of schizophrenia.

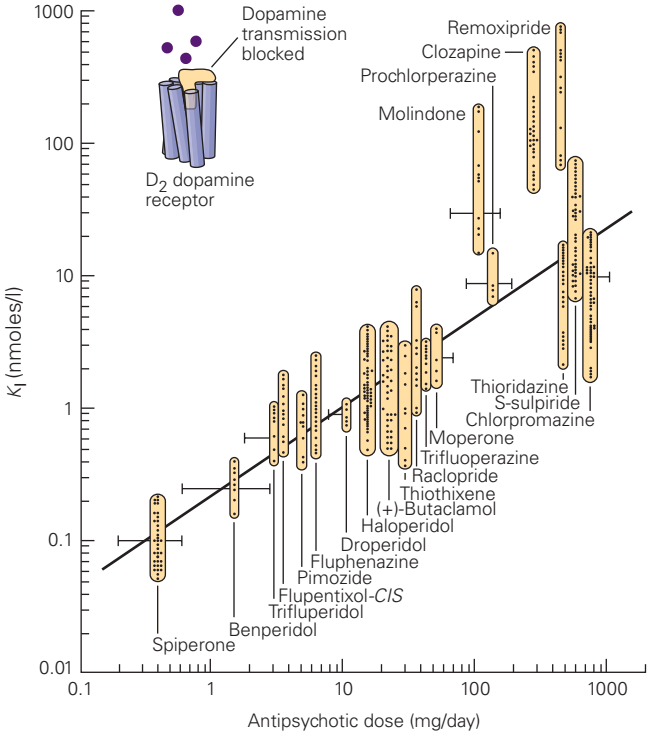

Figure 60–8 **The potency of first-generation antipsychotic drugs in treating psychotic symptoms correlates strongly with their affinity for D_2 dopamine receptors.** On the horizontal axis is the average daily dose required to achieve similar levels of clinical efficacy. On the vertical axis is K_i, the concentration of drug required to bind 50% of D_2 receptors in vitro. The higher the drug concentration required, the lower is the affinity of the drug for the receptor. One caveat is that the measurements on the two axes were not entirely independent of each other, as the ability of a drug to block D_2 receptors in vitro was often used to help determine doses used in clinical trials. Clozapine, which does not fall on the line, has significantly greater efficacy than the others. The mechanism of its greater efficacy is not understood. (Adapted, with permission, from Seeman et al. 1976.)

Among their side effects, chlorpromazine and related drugs caused Parkinson-like motor symptoms. Because Parkinson disease is caused by the loss of dopaminergic neurons in the midbrain, the occurrence of Parkinson-like side effects suggested to Arvid Carlsson that these drugs acted by decreasing 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 and activates a hyperpolarizing K^+ channel. A second signaling pathway for D_2 receptors is mediated by β-arrestin. The D_1 receptor is expressed in the striatum and is the major class of dopamine receptor in the cerebral cortex and hippocampus. The D_2 receptor is expressed most densely in the striatum, cerebral cortex, amygdala, and hippocampus. Correlations between receptor binding studies and clinical efficacy on psychotic symptoms indicated that the D_2 family is the molecular target for the therapeutic actions of antipsychotic drugs.

Clozapine, an antipsychotic drug discovered in 1959, had a low liability for causing Parkinson-like motor side effects. However, because it had some severe side effects, including a small chance of causing a potentially lethal loss of blood granulocytes, its use was discontinued until a clinical trial in the late 1980s clearly showed that it had greater efficacy than other antipsychotic drugs. Clozapine caused improvement in some individuals who had not responded to other antipsychotic drugs. It was reintroduced in conjunction with weekly monitoring of white cell counts; attempts to equal the efficacy of clozapine also motivated the development of second-generation antipsychotic drugs that mimicked some of its receptor binding properties, notably the ability to block serotonin 5-HT_{2A} receptors, an action that appears to diminish motor side effects. Large-scale clinical trials of the second-generation antipsychotic drugs have shown that their efficacy is no greater than the first-generation drugs, with none

having efficacy equal to clozapine. The liability of second-generation drugs for causing Parkinson-like motor side effects is lower than that of the first generation, but they typically cause more severe weight gain and other metabolic problems.

Because drugs that reduce psychotic 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 when taken chronically at high doses. Thus, Carlsson suggested that dopaminergic systems are hyperactive in schizophrenia. Evidence for this hypothesis has been difficult to obtain. The most direct evidence for this idea comes from studies begun in the mid-1990s that found that amphetamine-induced increases in dopamine release were greater in patients with schizophrenia 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—may lead to hyperactivity in the subcortical dopaminergic systems and could contribute to the psychotic symptoms of schizophrenia, the symptoms that respond to antipsychotic drugs.

Although dopamine activity may increase in subcortical regions of the brain in schizophrenia, it may decrease in cortical regions; such a decrease might contribute to the cognitive impairments seen in schizophrenia. In particular, there may be fewer D_1 receptors in the prefrontal cortex in schizophrenia, which would be consistent with the observation that D_1 receptors in the prefrontal cortex normally play a role in working memory and in executive functions.

Highlights

1. Schizophrenia is a chronic, profoundly disabling disorder characterized by dramatic psychotic symptoms as well as deficits in emotion, motivation, and cognition.
2. Risk for schizophrenia is an inherited, polygenic trait.
3. Antipsychotic drugs are effective in reducing hallucinations, delusions, and thought disorder but do not benefit the cognitive and deficit symptoms of schizophrenia.
4. Cognitive impairments reduce the ability of people with schizophrenia to regulate their behavior in accordance with their goals. As a result, people with schizophrenia are frequently unable to succeed in school or to hold down jobs, even at times when antipsychotic drugs effectively control their hallucinations and delusions.
5. Postmortem and neuroimaging studies document loss of gray matter in the prefrontal and temporal cerebral cortex in a pattern that is consistent with cognitive impairments, such as deficits in working memory.
6. The gray matter loss results from decreased dendritic arborization and decreased dendritic spines, which implies that synaptic connections are also reduced. One hypothesis consistent with these anatomic findings and with the typical age of onset in adolescence is that schizophrenia is triggered by excessive and inappropriate synaptic pruning in the prefrontal and temporal cerebral cortices during adolescence and young adulthood.
7. Progress in the genetic analysis of schizophrenia combined with the use of new tools to study systems-level neuroscience promises to help attain the much needed advances in understanding disease mechanisms and in discovering new therapeutics.

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